REMARKS

Claims 4, 6 and 19 are now pending in this application. The amendments to the claims are similar to those proposed in the Amendment After Final filed on October 6, 2004. The exception being that claim 7 has now been canceled, claim 4 now recites the administration of ramipril or ramiprilat, and claims 6 and 19 have been amended to more properly depend from amended claim 4. These amendments do not raise issues and should not necessitate a new search. Previous claims 6 and 19 already specifically identified the administration of ramipril and ramiprilat.

As indicated in the Advisory Action dated November 3, 2004, the amendments proposed on October 6, 2004 were not entered. The continuation sheet attached to the Advisory Action states that the amendments were not entered because the amended claims were not supported by the specification. In particular, the Examiner stated that the specification did not literally support the treatment of a "human" who exhibits normal or low blood pressure.

The undersigned spoke with the Examiner by telephone on November 5, 2004, to discuss this question of written description support, and the Examiner invited the undersigned to provide comments on the issue in this supplemental paper. The following comments relate only to the question of written description support of the amended claims. Arguments as to why the amended claims are patentable in view of certain cited references were presented in the earlier Amendment After Final and are not repeated here.

The "fundamental factual inquiry" in the written description analysis is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163.02. The specification provides written description support for the amended claims, including support for the treatment of a "human" who exhibits normal or low blood pressure. For instance, the specification in the fourth full paragraph on page 3 mentions that a suitable definition of normal or low blood pressure can be found in JNC VI, which was incorporated by reference. A copy of JNC VI is attached to this Amendment for the Examiner's review. It is clear that the entire document concerns the study, detection and prevention of hypertension in human men, women, and children. Table 2 on page 11 of the attachment illustrates a classification of blood pressure for "adults age 18 and older." Page 12 of the attachment discusses techniques for blood pressure measurement of patients, as

well as instructions to clinicians to explain to patients the meaning of their blood pressure readings. There should be no question at all that these patients are human. The patent specification obviously conveys the treatment of humans by referring to the JNC VI disclosure for a suitable definition of normal or low blood pressure.

Applicants believe that the pending claims should be in condition for allowance. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

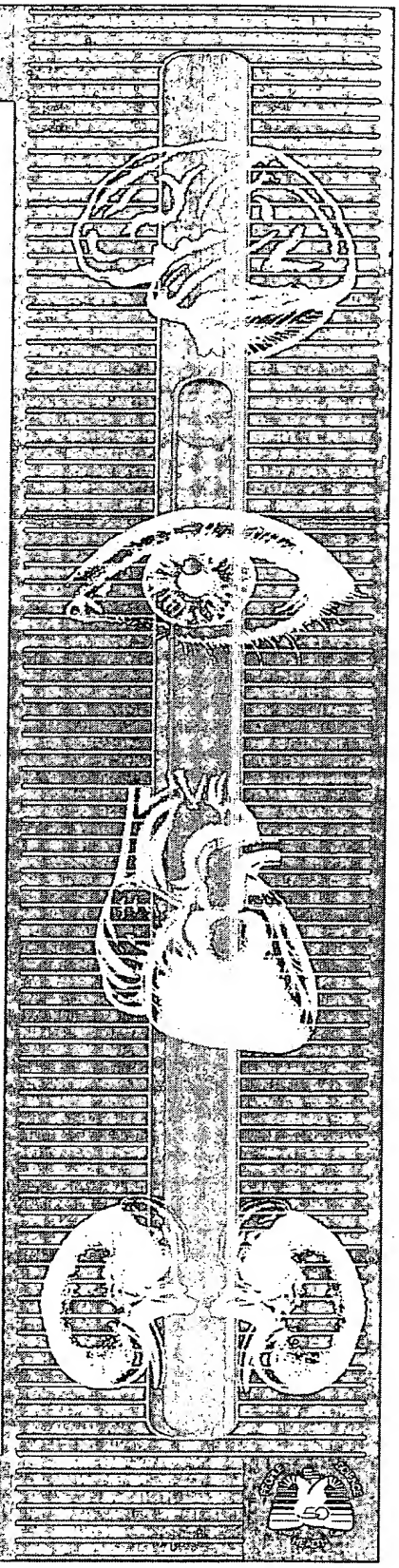
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 6, 2004

By: _____
Steven J. Scott
Reg. No. 43,911

National High Blood Pressure Education Program

The Sixth Report of the JOINT NATIONAL COMMITTEE on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure



NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

National Institutes of Health

National Heart, Lung, and Blood Institute

National High Blood Pressure Education Program

NIH Publication

No. 98-4080

November 1997

ACKNOWLEDGMENTS

CHAIR

Sheldon G. Sheps, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN)

EXECUTIVE COMMITTEE

Henry R. Black, MD, Chair of Chapter 1 (Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL); Jerome D. Cohen, MD, Chair of Chapter 2 (St. Louis University Health Sciences Center, St. Louis, MO); Norman M. Kaplan, MD, Chair of Chapter 3 (University of Texas Southwestern Medical School, Dallas, TX); Keith C. Ferdinand, MD, Chair of Chapter 4 (Heartbeats Life Center, New Orleans, LA); Aram V. Chobanian, MD (Boston University, Boston, MA); Harriet P. Dustan, MD (University of Vermont College of Medicine, Burlington, VT); Ray W. Gifford, Jr., MD (Cleveland Clinic Foundation, Cleveland, OH); Marvin Moser, MD (Yale University School of Medicine, New Haven, CT); Sheldon G. Sheps, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN).

CONTRIBUTORS

Lawrence Agodoa, MD (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD); Phyllis A. August, MD (New York Hospital, New York, NY); George L. Bakris, MD (Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL); Vicki Burt, RN, ScM (National Center for Health Statistics, Hyattsville, MD); William Busse, MD (University of Wisconsin, Madison, WI); Barry L. Carter, PharmD (University of Colorado, Denver, CO); Francis D. Chesley, MD (Agency for Health Care Policy and Research, Rockville, MD); James Cleeman, MD (National Heart, Lung, and Blood Institute, Bethesda, MD); Jay N. Cohn, MD (University of Minnesota Medical School, Minneapolis, MN); Louis L. Cregler, MD (City University of New York Medical School, New York, NY); Carlos Crespo, DrPH, MS (American University, Washington, DC); William C. Cushman, MD (University of Tennessee College of Medicine, Memphis, TN); Jeffrey Cutler, MD, MPH (National Heart, Lung, and Blood Institute, Bethesda, MD); Mark D. Darrow, MD (East Carolina University School of Medicine, Greenville, NC); Vincent L. DeQuattro, MD (University of Southern California Medical Center, Los Angeles, CA); Richard B. Devereux, MD (Cornell University Medical Center, New York, NY); Lance D. Dworkin, MD (Rhode Island Hospital, Providence, RI); William J. Elliott, MD, PhD (Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL); Murray Epstein, MD (University of Miami School of Medicine, Miami, FL); Bonita Falkner, MD (Allegheny University of the Health Sciences, Philadelphia, PA); Carlos M. Ferrario, MD (Bowman Gray School of Medicine, Winston-Salem, NC); John M. Flack, MD, MPH (Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, NC); William Frishman, MD (Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY); Edward D. Frohlich, MD (Alton Ochsner Medical Foundation, New Orleans, LA); Lee A. Green, MD, MPH (University of Michigan, Ann Arbor, MI); Richard H. Grimm, Jr., MD, PhD (University of Minnesota Medical School, Minneapolis, MN); James M. Hagberg, PhD (University of Maryland, College Park, MD); W. Dallas Hall, MD (Emory University, Atlanta, GA); Joel Handler, MD (Kaiser Permanente, Anaheim, CA); Stephen Havas, MD, MPH, MS (University of Maryland School of Medicine, Baltimore, MD); Martha N. Hill, PhD, MSN (Johns Hopkins University, Baltimore, MD); Michael J. Horan, MD, ScM (National Heart, Lung, and Blood Institute, Bethesda, MD); Willa A. Hsueh, MD (University of Southern California Medical Center, Los Angeles, CA); Barry N. Hyman, MD (Baylor College of Medicine, Houston, TX); Joseph L. Izzo, Jr., MD (State University of New York, Buffalo, NY); Kenneth Jamerson, MD (University of Michigan Medical Center, Ann Arbor, MI); James P. Kiley, PhD (National Heart, Lung, and Blood Institute, Bethesda, MD); Mehendr S. Kochar, MD, MS (Medical College of Wisconsin, Milwaukee, WI); Kathryn M. Kolasa, PhD, RD, LDN (East Carolina University School of Medicine, Greenville, NC); Lawrence R. Krakoff, MD (Englewood Hospital, Englewood, NJ); Daniel Levy, MD (Framingham Heart Study, National Heart, Lung, and Blood Institute, Framingham, MA); Marshall D. Lindheimer, MD (University of Chicago Hospitals, Chicago, IL); Russell V. Luepker, MD (University of Minnesota, Minneapolis, MN); Mary E. Leavell Malone, MA, MSN (Jefferson Community College, Louisville, KY); Barry Massie, MD (University of California, San Francisco, CA); Barry J. Materson, MD, MBA (University of Miami, Miami, FL); Jay Merchant, MHA (Health Care Financing Administration, Washington, DC); Franz H. Messerli, MD (Ochsner Clinic and Alton Ochsner Medical Foundation, New Orleans, LA); Nancy Houston Miller, BSN (Stanford Cardiac Rehabilitation Program, Palo Alto, CA); Michael A. Moore, MD (Bowman Gray School of Medicine, Winston-Salem, NC); Lisa Mustone-Alexander, MPH, PA (George Washington University School of Medicine and Health Sciences, Washington, DC); Suzanne Oparil, MD (University of Alabama at Birmingham, Birmingham, AL); Vasilios Papademetriou, MD (Veterans Affairs Medical Center, Washington, DC); H. Mitchell Perry, Jr., MD (Washington University School of Medicine, St. Louis, MO); Thomas G. Pickering, MD, DPhil (Cornell University Medical Center, New York, NY); J. Howard Pratt, MD (Indiana University School of Medicine, Indianapolis, IN); C. Venkata S. Ram, MD (University of Texas Southwestern Medical Center, Dallas, TX); Otelio S. Randall, MD (Howard University

Hospital, Washington, DC); James W. Reed, MD (Morehouse School of Medicine, Atlanta, GA); Raymond W. Roberts, PharmD (Vencor, Louisville, KY); Edward J. Roccella, PhD, MPH (National Heart, Lung, and Blood Institute, Bethesda, MD); Susan D. Rogus, RN, MS (National Heart, Lung, and Blood Institute, Bethesda, MD); Elijah Saunders, MD (University of Maryland, Baltimore, MD); Eleanor Schron, RN, MSN (National Heart, Lung, and Blood Institute, Bethesda, MD); Gary Schwartz, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); Baha M. Sibai, MD (University of Tennessee College of Medicine, Memphis, TN); David Snyder, RPh, DDS (Health Resources and Services Administration, Rockville, MD); James R. Sowers, MD (Wayne State University, Detroit, MI); Jeremiah Stamler, MD (Northwestern University Medical School, Chicago, IL); Robert Temple, MD (Food and Drug Administration, Rockville, MD); Steve Textor, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); Thomas Thom, BA (National Heart, Lung, and Blood Institute, Bethesda, MD); Donald G. Vidt, MD (Cleveland Clinic Foundation, Cleveland, OH); Michael Weber, MD (Brookdale Hospital, Brooklyn, NY); Myron H. Weinberger, MD (Indiana University School of Medicine, Indianapolis, IN); Richard Weinshilboum, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); Paul K. Whelton, MD, MSc (Tulane University School of Public Health and Tropical Medicine, New Orleans, LA); Jack P. Whisnant, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); David O. Wiebers, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); Mary C. Winston, EdD, RD (American Heart Association, Dallas, TX); Jackson T. Wright, Jr., MD, PhD (Case Western Reserve University, Cleveland, OH).

National High Blood Pressure Education Program Coordinating Committee

Claude Lenfant, MD, Chair (National Heart, Lung, and Blood Institute); Henry R. Black, MD (American Heart Association); Vicki Burt, RN, ScM (National Center for Health Statistics, Centers for Disease Control and Prevention); Barry L. Carter, PharmD (American Society of Health-System Pharmacists); Linda Casser, OD (American Optometric Association); Francis D. Chesley, MD (Agency for Health Care Policy and Research); Jerome D. Cohen, MD (American College of Physicians); Pamela J. Colman, DPM (American Podiatric Medical Association); Thelma Edwards, RN (National Stroke Association); Murray Epstein, MD (National Kidney Foundation); Donna M. Feeley, MPH (American Red Cross); Keith Copelin Ferdinand, MD (National Heart, Lung, and Blood Institute Ad Hoc Committee on Minority Populations); Edward D. Frohlich, MD (American College of Cardiology); Jerzy Gajewski, MD, PhD (American Academy of Insurance Medicine); Ray W. Gifford, Jr., MD (American Medical Association); Lee A. Green, MD, MPH (American Academy of Family Physicians); Stephen Havas, MD, MPH, MS (American Public Health Association); Caroline Haynes, RN, MPH, COHN (American Association of Occupational Health Nurses); Barry N. Hyman, MD (American Academy of Ophthalmology); Joseph L. Izzo, Jr., MD (Council on Geriatric Cardiology); Norman M. Kaplan, MD (American Society of Hypertension); Kathryn M. Kolasa, PhD, RD, LDN (Society for Nutrition Education); David Levine, MD, ScD, MPH (American College of Preventive Medicine); Mary E. Leavell Malone, MA, MSN (National Black Nurses' Association); William Manger, MD, PhD (National Hypertension Association); Edwin C. Marshall, OD, MPH (National Optometric Association); Jay Merchant, MHA (Health Care Financing Administration); Nancy Houston Miller, BSN (American Nurses' Association); Marvin Moser, MD (National High Blood Pressure Education Program); Lisa Mustone-Alexander, MPH, PA (American Academy of Physician Assistants); William A. Nickey, DO (American Osteopathic Association); H. Mitchell Perry, Jr., MD (U.S. Department of Veterans Affairs); Otelio S. Randall, MD (National Medical Association); James W. Reed, MD (International Society on Hypertension in Blacks); Raymond W. Roberts, PharmD (American Pharmaceutical Association); Brodie G. Secrest, Jr., DDS (American Dental Association); Sheldon G. Sheps, MD (American College of Chest Physicians); Elizabeth H. Singer, MS (National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD); David Snyder, RPh, DDS (Health Resources and Services Administration); James R. Sowers, MD (American Diabetes Association); Jack P. Whisnant, MD (American Academy of Neurology); Gerald J. Wilson, MA, MBA (Citizens for Public Action on High Blood Pressure and Cholesterol); Mary C. Winston, EdD, RD (American Dietetic Association); Jackson T. Wright, Jr., MD, PhD (Association of Black Cardiologists); Joyce M. Young, MD (American College of Occupational and Environmental Medicine).

Reviewers

John W. Bachman, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN); Vito M. Campese, MD (University of Southern California Medical Center, Los Angeles, CA); Albert A. Carr, MD (Circulatory Disease Center—Augusta Preventive Cardiology, Augusta, Georgia); Mary Hand, MSPH, RN (National Heart, Lung, and Blood Institute, Bethesda, MD); David C. Holden, MD (Family Practice, Peoria, IL); Michael J. Jamieson, MD (University of Texas Health Sciences Center, San Antonio, TX); Stevo Julius, MD (University of Michigan Medical Center, Ann Arbor, MI); George A. Mensah, MD (Medical College of Georgia, Augusta, GA); L. Michael Prisant, MD (Medical College of Georgia, Augusta, GA); Jay M. Sullivan, MD (University of Tennessee, Memphis, TN); Daniel J. Wilson, MD (Mayo Clinic and Mayo Foundation and Mayo Medical School, Rochester, MN).

Staff

Edward J. Roccella, PhD, MPH (National Heart, Lung, and Blood Institute, Bethesda, MD); Gregory Morosco, PhD, MPH (National Heart, Lung, and Blood Institute, Bethesda, MD); Darrell E. Anderson, MS (R.O.W. Sciences, Inc., Rockville, MD); Debra Waugh, BA (R.O.W. Sciences, Inc., Rockville, MD).

TABLE OF CONTENTS

List of Tables

List of Figures

FOREWORD

The purpose of the *Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC VI) is to provide guidance for primary care clinicians. The committee recognizes that the responsible clinician's judgment of the individual patient's needs remains paramount. Therefore, this national guideline should serve as a tool to be adapted and implemented in local and individual situations. Using evidence-based medicine and consensus, the report updates contemporary approaches to hypertension control. Among the issues covered are the important need for prevention of high blood pressure by improving lifestyles, the cost of health care, the use of self-measurement of blood pressure, the role of managed care in the treatment of high blood pressure, the introduction of new combination antihypertensive medications and angiotensin II receptor blockers, and strategies for improving adherence to treatment. The JNC VI report places more emphasis than earlier reports on absolute risk and benefit and uses risk stratification as part of the treatment strategy. This report strongly encourages lifestyle modification to prevent high blood pressure, as definitive therapy for some, and as adjunctive therapy for all persons with hypertension. On the basis of outcomes data from randomized controlled trials, this report recommends starting pharmacologic therapy with diuretics and beta-blockers for patients with uncomplicated hypertension and provides compelling indications for specific agents in certain clinical situations. This document also states that it is appropriate to choose other classes of antihypertensive agents in certain clinical situations and in patients with comorbid conditions. The National High Blood Pressure Education Program Coordinating Committee will release other advisories as the scientific evidence becomes available.

Dr. Sheldon Sheps is to be congratulated for leading the efforts to develop this document. He, along with the executive committee, worked diligently and brilliantly to assemble this report. This is evidence of how to use available science to develop practical guidelines for busy clinicians.

Claude Lenfant, M.D.
Director
National Heart, Lung, and Blood Institute

CHAPTER 1

INTRODUCTION

The National High Blood Pressure Education Program (NHBPEP), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health, was established in 1972. The program is succeeding in its mission of increasing awareness, prevention, treatment, and control of hypertension (table 1). From the 1976-80 National Health and Nutrition Examination Survey (NHANES II) to the 1988-91 survey (NHANES III, phase 1), the percentage of Americans who are aware that they have high blood pressure increased from 51 to 73 percent.[1] Among persons with hypertension, treatment has increased during that same period from 31 to 55 percent. The number of persons with high blood pressure controlled to below 140/90 mm Hg has increased from 10 percent in the NHANES II to 29 percent in the NHANES III, phase 1.[1]

These changes have contributed to dramatic reductions in morbidity and mortality attributable to hypertension. For example, age-adjusted death rates from stroke have declined by nearly 60 percent and from coronary heart disease (CHD) by 53 percent. These trends are evident in men and women and in African Americans and whites (figures 1 and 2). The benefit of reduction in stroke mortality is particularly striking in women age 50 and older: one-half of the benefit among white women and nearly two-thirds of the benefit among African American women can be attributed to the fall in blood pressure.[2] These improvements are consistent with the decline in disability among older Americans and have important implications for reducing national health care costs.[3]

Table 1

TRENDS IN THE AWARENESS, TREATMENT, AND CONTROL OF HIGH BLOOD PRESSURE IN ADULTS: UNITED STATES, 1976-94*

	NHANES II (1976-80)	NHANES III (Phase 1) 1988-91	NHANES III (Phase 2) 1991-94
Awareness	51%	73%	68.4%
Treatment	31%	55%	53.6%
Control†	10%	29%	27.4%

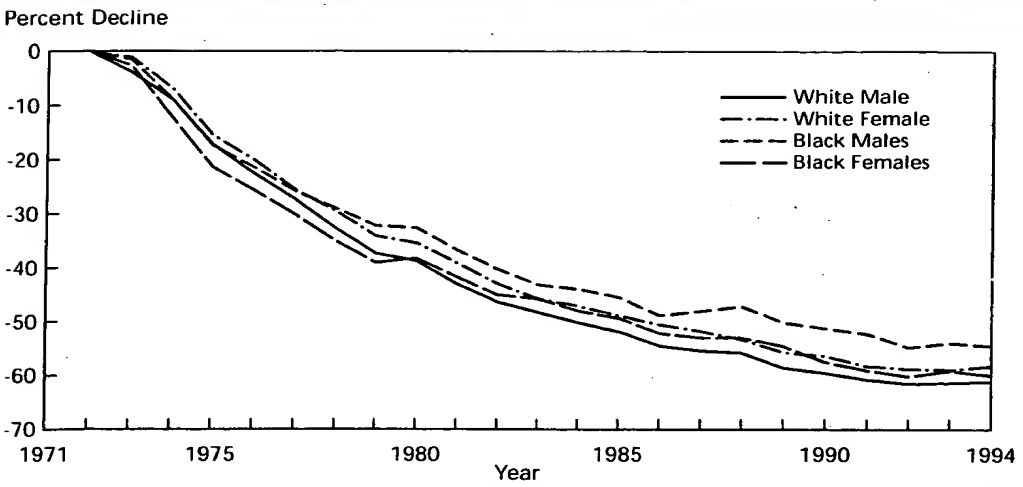
* Data are for adults age 18 to 74 years with SBP of 140 mm Hg or greater, DBP of 90 mm Hg or greater, or taking antihypertensive medication.

† SBP below 140 mm Hg and DBP below 90 mm Hg.

Source: Burt V et al.[1] and unpublished NHANES III, phase 2, data provided by the Centers for Disease Control and Prevention, National Center for Health Statistics.[2]

Figure 1

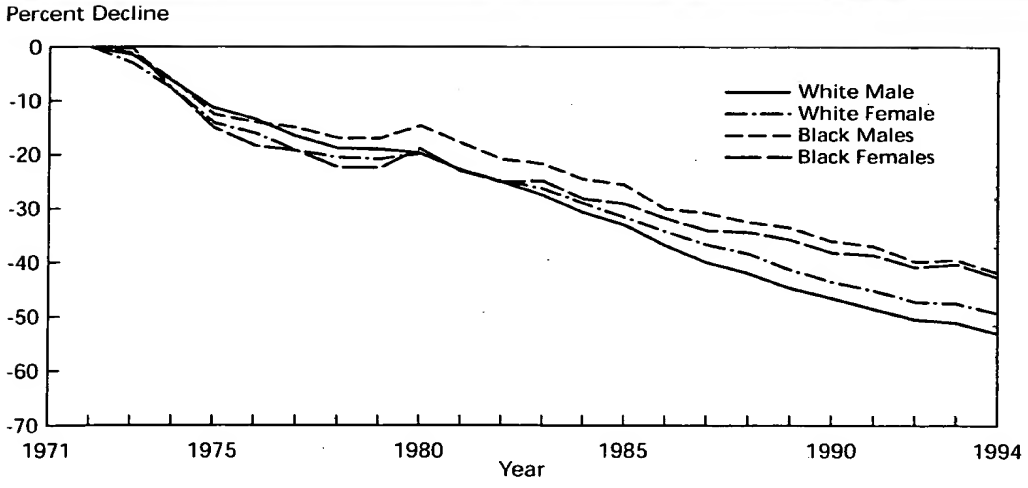
Percent Decline in Age-Adjusted Mortality Rates for Stroke by Sex and Race: United States, 1972-94



Source: Prepared by the NHLBI using data from *Vital Statistics of the United States*, National Center for Health Statistics. Age-adjusted to the 1940 U.S. census population. The decline in age-adjusted mortality from stroke in the total population is 59.0 percent.

Figure 2

Percent Decline in Age-Adjusted Mortality Rates for CHD by Sex and Race: United States, 1972-94



However, since publication of the *Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure* (JNC V),[4] these dramatic improvements have slowed; since 1993, age-adjusted stroke rates have risen slightly, and the slope of the age-adjusted rate of decline in CHD appears to be leveling.[5] Furthermore, rates have increased for both the incidence of end-stage renal disease, for which high blood pressure is the second most common antecedent,[6] and the prevalence of heart failure, wherein the large majority of patients have antecedent hypertension[7] (figures 3 and 4). Moreover, hypertension control rates have not continued to improve (NHANES III, phase 2) (table 1). If awareness, treatment, and control rates had continued the trend established between 1976-80 and 1988-91, there would have been an increase in 1991-94 in awareness to 76.2 percent, in treatment to 59.6 percent, and in control to 31.2 percent instead of the levels shown in table 1.[8] In addition, recent reports from Minnesota have shown a decrease in awareness, treatment, and control of hypertension.[9-11]

Organization and Method

The NHBPEP Coordinating Committee consists of representatives from 38 national professional, public, and voluntary health organizations and 7 Federal agencies. After this committee ascertained the need for a JNC VI report, NHLBI staff conducted and reported on focus groups among primary care physicians regarding the nature and purpose of national guidelines and to determine how the guidelines could best be structured to help busy clinicians. These focus groups recommended that guidelines for busy clinicians must be succinct and user-friendly.[15]

The preparation of the JNC VI report was coordinated by an executive committee, composed of the JNC VI chair, the chairs of the individual chapter writing teams, and the chairs of four previous JNC reports—a total of nine individuals. Contributions were obtained from multidisciplinary experts from the fields of medicine, nursing, nutrition, pharmacy, and public health, whose submissions were condensed, assembled, reviewed, and edited by the executive committee.

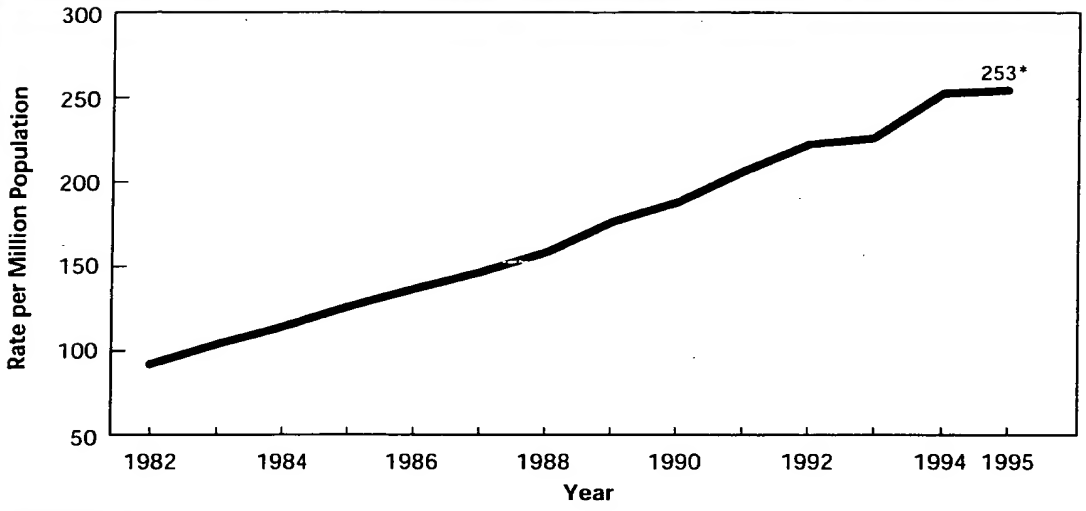
The contributing team members were asked to review the English-language literature on hypertension published since January 1992 for their sections. Previous literature was reviewed in earlier reports. However, in some instances, earlier literature was included to strengthen evidence-based recommendations. Inclusion decisions were made by the same experts. The data have been synthesized into recommendations by consensus of the executive committee, which considered the nature and quality of the study designs and analyses. Additional experts in specific areas were consulted as needed. Each contributor had the opportunity to review and comment on the entire document.

The executive committee met in person on six occasions, conducted several teleconferences, and had extensive correspondence. The executive committee used a modified nominal group process to identify and resolve issues.[16] On behalf of the executive committee, the JNC VI chair reported to the NHBPEP Coordinating Committee, which reviewed the document at its spring 1997 meeting and submitted written comments to the executive committee. The Coordinating Committee had the final vote of approval on the report.

The development of this report was funded entirely by the NHLBI. The executive committee, contributors, reviewers, and Coordinating Committee members served as volunteers and were remunerated only for travel expenses pertaining to Coordinating Committee and executive committee meetings.

Figure 3

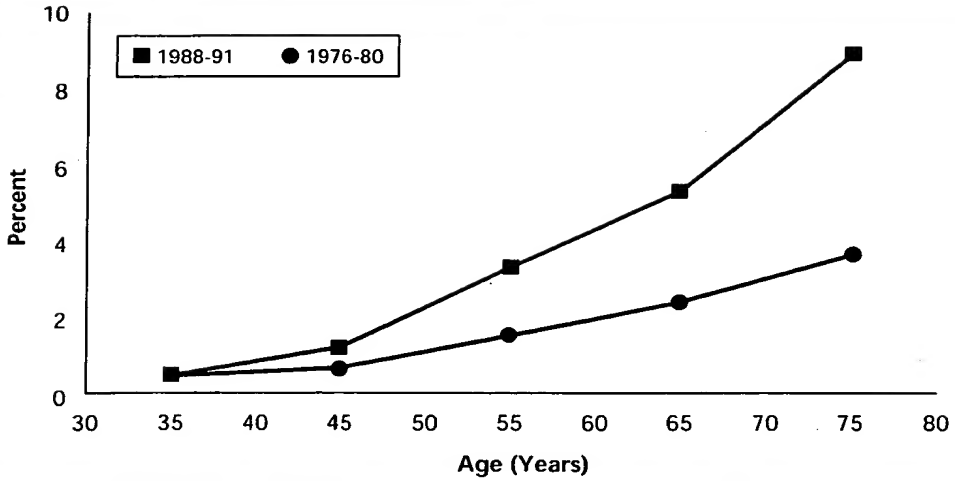
Incidence Rates per Million Population of Reported End-Stage Renal Disease Therapy, 1982-95, Adjusted for Age, Race, and Sex



*Provisional data.
Source: U.S. Renal Data System, 1997.[6]

Figure 4

Prevalence of Heart Failure, by Age, 1976-80 and 1988-91



Source: National Health and Nutrition Examination Survey (1976-80 and 1988-91), National Center for Health Statistics.

Furthermore, the average blood pressure of a cohort in Iowa that has been serially evaluated and age-adjusted has risen.[12] Progress has been steady toward reaching the U.S. Department of Health and Human Services goals for heart disease and stroke, but additional efforts are necessary to meet these objectives by the year 2000.[13]

Heart disease and stroke remain the first and third leading causes of death, respectively, in the United States and impose an enormous financial and social burden on Americans (more than $259 billion in direct and indirect costs).[5] In particular, the continued high prevalence of hypertension and hypertension-related complications of stroke, heart failure, and end-stage renal disease in the southeastern United States makes these diseases a public health concern for all who reside in this region, particularly African Americans.[14] These disturbing trends support the need to enhance public and professional education and to translate the results of research into improved health.

Evidence Base

The studies that provided evidence supporting the recommendations for prevention and treatment (chapters 3 and 4) were classified by the writers and staff and reviewed by the chapter chairs. For the purpose of this report, the classification was adapted from Last and Abramson[17] as follows:

M meta-analyses—an analysis of a compendium of experimental studies;

Ra randomized controlled trials—also known as experimental studies;

Re retrospective analyses—also known as case control studies;

F prospective followup—also known as cohort studies, including historical cohort studies and long-term followup;

X cross-sectional population studies—also known as prevalence studies;

Pr previous review or position statements; and

C clinical interventions (nonrandomized).

These symbols follow the references in the reference list of the report as well as the citations in chapters 3 and 4 in the text. Some references may have more than one code depending on the component of the study cited (e.g., a randomized controlled trial having a long-term followup).

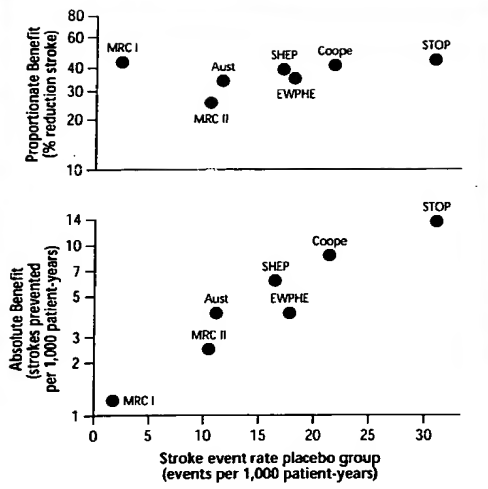
Clinical Policy

In considering the evidence to formulate clinical policy, absolute rather than relative changes were considered because the absolute benefit derived from treating hypertension depends on the absolute risk; that is, those at greater risk will achieve greater benefit[18] (figure 5). Information from randomized controlled trials (RCTs) indicates the reduction in the number of cardiovascular events in a known time period among patients with defined hypertension. The inverse of absolute risk reduction is the number of patients needed to be treated to prevent one event.[19] In the clinical policy presented below, the JNC report emphasizes interventions that have been shown to reduce the incidence of adverse clinical outcomes, mostly from RCTs, which remain the best source of evidence. Nonetheless, RCTs do have limitations,[20-23] which are summarized as follows:

- RCTs are of short to moderate duration, and benefits of hypertension treatment accrue over a lifetime.
- Most RCTs do not include a true placebo group, thus underestimating the beneficial effect of the trials. For example, the control group may include those receiving treatment according to protocol or by their personal clinician after commencement of the trial (the drop-in effect), the true effects of the treatment may be diluted by those who stopped it (the drop-out effect), or the trial is a comparison of two forms of therapy.
- RCTs do not truly represent clinical practice because some patients (typically those at higher risk) are excluded from trials, such as patients with recent stroke or myocardial infarction or patients with a specific need for

Figure 5

COMPARISON OF PROPORTIONATE (RELATIVE) AND ABSOLUTE BENEFIT FROM REDUCTION IN THE INCIDENCE OF STROKE



Comparison of proportionate (relative) and absolute benefit from reduction in the incidence of stroke in six trials under review and in one other with a similar design but in which the absolute risk of stroke was much lower. Event rates are for fatal and nonfatal stroke combined. It is the relative constancy of the proportionate benefit (top), coupled with the wide range of risk in controls (abscissa), that produces both the wide range of risk and absolute benefit in these trials and the relationship of risk and absolute benefit (bottom). MRC I indicates Medical Research Council trial I; MRC II, MRC trial II; Aust, Australian study; SHEP, Systolic Hypertension in the Elderly Program; EWPHE, European Working Party on High Blood Pressure in the Elderly trial; Coope, Coope and Warrender; and STOP, Swedish Trial in Old Patients with Hypertension.

Source: Lever and Ramsay.[18]

the study drug (e.g., beta-blockers). Thus, the study cohort may be at lower risk than the general population.

- The average reduction in blood pressure in RCTs is modest and underestimates the additional benefits that accrue from larger decreases in blood pressure, which may be seen in individual patients.
- RCTs focus primarily on *a priori* endpoints and not necessarily on other benefits of therapy (e.g., prevention of progression to disease endpoints, improved quality of life, reduced impact of comorbid conditions, fewer workdays missed because of illness).
- Finally, the methods used in constructing meta-analyses vary by author; thus, the conclusions (e.g., number of patients needed to treat to prevent one event) may differ.

Because of these limitations, the executive committee extrapolated treatment effects beyond the duration of the clinical trials based on physiological and epidemiological data.

PUBLIC HEALTH CHALLENGES OF HYPERTENSION

The prevention and treatment of hypertension represent major public health challenges for the United States as we enter the new millennium. These are the challenges:

- **Prevent the rise of blood pressure with age.** If the U.S. population retained the average blood pressure levels of young adults, there would be less cardiovascular disease.
- **Decrease the existing prevalence of hypertension.** Approximately 50 million adult Americans have hypertension.[24]
- **Increase hypertension awareness and detection.** A large number of adult Americans with hypertension are still unaware that they have high blood pressure.[24]
- **Improve control of hypertension.** Nearly three-fourths of adult Americans with hypertension are not controlling their blood pressure to below 140/90 mm Hg.[24]
- **Reduce cardiovascular risks.** Most persons with hypertension have additional risk factors for cardiovascular disease.[25]
- **Increase recognition of the importance of controlled isolated systolic hypertension.** The majority of persons with isolated systolic hypertension are not adequately controlling their blood pressure despite persuasive data from clinical trials documenting the benefit of treatment.[24]

- **Improve recognition of the importance of high-normal blood pressure.** The impact of high-normal blood pressure—systolic blood pressure of 130 to 139 mm Hg and diastolic blood pressure of 85 to 89 mm Hg—on the development of hypertension and target organ damage remains unappreciated.[26,27]
- **Reduce ethnic, socioeconomic, and regional variations in hypertension.** Differences remain in the prevalence of hypertension, high-normal blood pressure, and cardiovascular events in different ethnic and socioeconomic groups and geographic regions.[14]
- **Improve opportunities for treatment.** Well-tolerated and affordable treatment options, including both lifestyle modifications and pharmacologic treatment, are not being universally applied.[14]
- **Enhance community programs.** In the face of declining budgets, community programs are challenged to increase activities to prevent high blood pressure and serve more persons with hypertension.

Community Programs

During its 25-year history, the NHBPEP has developed a broad array of community-based activities designed to promote prevention, raise awareness, screen for high blood pressure and other cardiovascular risk factors, improve adherence to therapy, and reduce morbidity and mortality. Community program activities are addressed fully in NHLBI publications and other documents.[28-39]

Summary

- Hypertension awareness, treatment, and control rates have increased over the past 3 decades. The rates of increase have lessened since publication of the JNC V report.
- Age-adjusted mortality rates for stroke and coronary heart disease declined during this time but now appear to be leveling.
- The incidence of end-stage renal disease and the prevalence of heart failure are increasing.
- Randomized controlled trials provide the best method of estimating the benefit of treatment and source of information for clinical policy, but they do have limitations.
- Prevention and treatment of hypertension and target organ disease remain important public health challenges that must be addressed.

CHAPTER 2

BLOOD PRESSURE MEASUREMENT AND CLINICAL EVALUATION

Hypertension is defined as systolic blood pressure (SBP) of 140 mm Hg or greater, diastolic blood pressure (DBP) of 90 mm Hg or greater, or taking antihypertensive medication. The objective of identifying and treating high blood pressure is to reduce the risk of cardiovascular disease and associated morbidity and mortality. To that end, it is useful to provide a classification of adult blood pressure for the purpose of identifying high-risk individuals and to provide guidelines for followup and treatment.

The positive relationship between SBP and DBP and cardiovascular risk has long been recognized. This relationship is strong, continuous, graded, consistent, independent, predictive, and etiologically significant for those with and without coronary heart disease.[40,41] Therefore, although classification of adult blood pressure is somewhat arbitrary, it is useful to clinicians who must make treatment decisions based on a constellation of factors including the actual level of blood pressure. Table 2 provides a classification of blood

Table 2

CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGE 18 AND OLDER*

Category	Systolic (mm Hg)		Diastolic (mm Hg)
Optimal†	<120	and	<80
Normal	<130	and	<85
High-normal	130-139	or	85-89
Hypertension‡			
Stage 1	140-159	or	90-99
Stage 2	160-179	or	100-109
Stage 3	≥180	or	≥110

* Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic blood pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For example, 160/92 mm Hg should be classified as stage 2 hypertension, and 174/120 mm Hg should be classified as stage 3 hypertension. Isolated systolic hypertension is defined as SBP of 140 mm Hg or greater and DBP below 90 mm Hg and staged appropriately (e.g., 170/82 mm Hg is defined as stage 2 isolated systolic hypertension). In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors. This specificity is important for risk classification and treatment (see table 5).

† Optimal blood pressure with respect to cardiovascular risk is below 120/80 mm Hg. However, unusually low readings should be evaluated for clinical significance.

‡ Based on the average of two or more readings taken at each of two or more visits after an initial screening.

pressure for adults (age 18 and older). These criteria are for individuals who are not taking antihypertensive medication and who have no acute illness. This classification is based on the average of two or more blood pressure readings taken in accordance with the following recommendations at each of two or more visits after an initial screening visit. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's blood pressure. The classification is slightly modified from the JNC V report in that stage 3 and stage 4 hypertension are now combined because of the relative infrequency of stage 4 hypertension.

Detection and Confirmation

Hypertension detection begins with proper blood pressure measurements, which should be obtained at each health care encounter. Repeated blood pressure measurements will determine whether initial elevations persist and require prompt attention or have returned to normal and need only periodic surveillance. Blood pressure should be measured in a standardized fashion using equipment that meets certification criteria.[42] The following techniques are recommended:

- Patients should be seated in a chair with their backs supported and their arms bared and supported at heart level. Patients should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.
- Under special circumstances, measuring blood pressure in the supine and standing positions may be indicated (see chapter 4).
- Measurement should begin after at least 5 minutes of rest.
- The appropriate cuff size must be used to ensure accurate measurement. The bladder within the cuff should encircle at least 80 percent of the arm. Many adults will require a large adult cuff.
- Measurements should be taken preferably with a mercury sphygmomanometer; otherwise, a recently *calibrated* aneroid manometer or a *validated* electronic device can be used.
- Both SBP and DBP should be recorded. The first appearance of sound (phase 1) is used to define SBP. The disappearance of sound (phase 5) is used to define DBP.
- Two or more readings separated by 2 minutes should be averaged. If the first two readings differ by more than 5 mm Hg, additional readings should be obtained and averaged.

Clinicians should explain to patients the meaning of their blood pressure readings and advise them of the need for periodic remeasurement. Table 3 provides followup recommendations based on the initial set of blood pressure measurements. More information regarding blood pressure measurement may be found in the American Heart Association's *Recommendations for Human Blood Pressure Determination by Sphygmomanometers*[43] and the American Society of Hypertension's *Recommendations for Routine Blood Pressure Measurement by Indirect Cuff Sphygmomanometry*.[44]

Self-Measurement of Blood Pressure

Measurement of blood pressure outside the clinician's office may provide valuable information for the initial evaluation of patients with hypertension and for monitoring the response to treatment. Self-measurement has four general advantages: (1) distinguishing sustained hypertension from "white-coat hypertension," a condition noted in patients whose blood pressure is consistently elevated in the physician's office or clinic but normal at other times; (2) assessing response to antihypertensive medication; (3) improving patient adherence to treatment; and (4) potentially reducing costs.[45] The blood pressure of persons with hypertension tends to be higher when measured in the clinic than outside of the office.[46] There is no universally agreed-on upper limit of normal home blood pressure, but readings of

Table 3

Recommendations for Followup Based on Initial Blood Pressure Measurements for Adults

Initial Blood Pressure (mm Hg)*		
Systolic	Diastolic	Followup Recommended†
<130	<85	Recheck in 2 years
130-139	85-89	Recheck in 1 year‡
140-159	90-99	Confirm within 2 months‡
160-179	100-109	Evaluate or refer to source of care within 1 month
≥180	≥110	Evaluate or refer to source of care immediately or within 1 week depending on clinical situation

* If systolic and diastolic categories are different, follow recommendations for shorter time followup (e.g., 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

† Modify the scheduling of followup according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

‡ Provide advice about lifestyle modifications (see chapter 3).

135/85 mm Hg or greater should be considered elevated.[45,47,48]

Choice of Monitors for Personal Use

Although the mercury sphygmomanometer is still the most accurate device for clinical use, it is generally not practical for home use. Therefore, either validated electronic devices or aneroid sphygmomanometers that have proven to be accurate according to standard testing[42,49,50] are recommended for use along with appropriate-sized cuffs. Finger monitors are inaccurate.[51] Periodically, the accuracy of the patient's device should be checked by comparing readings with simultaneously recorded auscultatory readings taken with a mercury device. Independent evaluations of the instruments available to patients are published from time to time.[52]

Ambulatory Blood Pressure Monitoring

A variety of commercially available monitors, which are reliable, convenient, easy to use, and accurate, now are available.[49,50] These monitors typically are programmed to take readings every 15 to 30 minutes throughout the day and night while patients go about their normal daily activities. The readings can then be downloaded onto a personal computer for analysis. Normal blood pressure values taken by ambulatory measurement (1) are lower than clinic readings while patients are awake (below 135/85 mm Hg); (2) are even lower while patients are asleep (below 120/75 mm Hg); and (3) provide measures of SBP and DBP load.[45,47] In the majority of individuals, blood pressure falls by 10 to 20 percent

during the night; this change is more closely related to patterns of sleep and wakefulness than to time of day, as illustrated by the blood pressure rhythm following the inverted cycle of activity in night-shift workers.[53]

Among persons with hypertension, an extensive and very consistent body of evidence indicates that ambulatory blood pressure correlates more closely than clinic blood pressure with a variety of measures of target organ damage such as left ventricular hypertrophy.[47] Prospective data relating ambulatory blood pressure to prognosis are limited to two published studies, which suggest that, in patients in whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may identify a group at relatively low risk of morbidity.[54-56]

Ambulatory blood pressure monitoring is most clinically helpful and most commonly used in patients with suspected "white-coat hypertension," but it is also helpful in patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic hypertension, and autonomic dysfunction.[45] However, this procedure should not be used indiscriminately such as in the routine evaluation of patients with suspected hypertension.

EVALUATION

Evaluation of patients with documented hypertension has three objectives: (1) to identify known causes of high blood pressure; (2) to assess the presence or absence of target organ damage and cardiovascular disease, the extent of the disease, and the response to therapy; and (3) to identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment. Data for evaluation are acquired through medical history, physical examination, laboratory tests, and other diagnostic procedures.

Medical History

A medical history should include the following:

- known duration and levels of elevated blood pressure;
- patient history or symptoms of CHD, heart failure, cerebrovascular disease, peripheral vascular disease, renal disease, diabetes mellitus, dyslipidemia, other comorbid conditions, gout, or sexual dysfunction;
- family history of high blood pressure, premature CHD, stroke, diabetes, dyslipidemia, or renal disease;
- symptoms suggesting causes of hypertension;
- history of recent changes in weight, leisure-time physical activity, and smoking or other tobacco use;
- dietary assessment including intake of sodium, alcohol, saturated fat, and caffeine;
- history of all prescribed and over-the-counter medications, herbal remedies, and illicit drugs, some of which may raise blood pressure or interfere with the effectiveness of antihypertensive drugs (see chapter 4);
- results and adverse effects of previous antihypertensive therapy; and
- psychosocial and environmental factors (e.g., family situation, employment status and working conditions, educational level) that may influence hypertension control.

Physical Examination

The initial physical examination should include the following:

- two or more blood pressure measurements separated by 2 minutes with the patient either supine or seated and after standing for at least 2 minutes in accordance with the recommended techniques mentioned earlier;
- verification in the contralateral arm (if values are different, the higher value should be used);

- measurement of height, weight, and waist circumference (see chapter 3);
- funduscopic examination for hypertensive retinopathy (i.e., arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes, hemorrhages and exudates,[57] disc edema);
- examination of the neck for carotid bruits, distended veins, or an enlarged thyroid gland;
- examination of the heart for abnormalities in rate and rhythm, increased size, precordial heave, clicks, murmurs, and third and fourth heart sounds;
- examination of the lungs for rales and evidence for bronchospasm;
- examination of the abdomen for bruits, enlarged kidneys, masses, and abnormal aortic pulsation;
- examination of the extremities for diminished or absent peripheral arterial pulsations, bruits, and edema; and
- neurological assessment.

Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy are tests to determine the presence of target organ damage and other risk factors. These routine tests include urinalysis, complete blood cell count, blood chemistry (potassium, sodium, creatinine, fasting glucose, total cholesterol, and high-density lipoprotein [HDL] cholesterol), and 12-lead electrocardiogram.

Optional tests include creatinine clearance, microalbuminuria, 24-hour urinary protein, blood calcium, uric acid, fasting triglycerides, low-density lipoprotein (LDL) cholesterol, glycosolated hemoglobin, thyroid-stimulating hormone, and limited echocardiography (see chapter 4) (to determine the presence of left ventricular hypertrophy). More complete assessment of cardiac anatomy and function by standard echocardiography, examination of structural alterations in arteries by ultrasonography, measurement of ankle/arm index,[58] and plasma renin activity/urinary sodium determination may be useful in assessing cardiovascular status in selected patients.

Identifiable Causes of Hypertension

Additional diagnostic procedures may be indicated to seek causes of hypertension, particularly in patients (1) whose age, history, physical examination, severity of hypertension, or initial laboratory findings suggest such causes; (2) whose blood pressures are responding poorly to drug therapy; (3) with well-controlled hypertension whose blood pressures begin to increase; (4) with stage 3 hypertension; and (5) with sudden onset of hypertension. For example, labile hypertension or paroxysms of hypertension accompanied by headache, palpitations, pallor, and perspiration suggest pheochromocytoma; abdominal bruits, particularly those that lateralize to the renal areas or have a diastolic component, suggest renovascular disease; abdominal or flank masses may be polycystic kidneys; delayed or absent femoral arterial pulses and decreased blood pressure in the lower extremities may indicate aortic coarctation; and truncal obesity with purple striae suggests Cushing syndrome. Examples of clues from the laboratory tests include unprovoked hypokalemia (primary aldosteronism), hypercalcemia (hyperparathyroidism), and elevated creatinine or abnormal urinalysis (renal parenchymal disease). Appropriate investigations should be conducted when there is a high index of suspicion of an identifiable cause.

Genetics of Hypertension

Blood pressure levels are correlated among family members, a fact attributable to common genetic background, shared environment, or lifestyle habits.[59] High blood pressure appears to be a complex trait that does not follow the classic Mendelian rules of inheritance attributable to a single gene locus; the currently documented exceptions are a few rare forms of hypertension, such as those related to a single mutation involving a chimeric 11-beta-hydroxylase/aldosterone synthase gene.[60] High blood pressure appears to be a polygenic and multifactorial disorder in

which the interaction of several genes with each other and with the environment is important.[61] Potential candidate genes suggested by recent experimental data include those that affect various components of the renin-angiotensin-aldosterone system, the kallikrein-kinin system, and the sympathetic nervous system.

Table 4

COMPONENTS OF CARDIOVASCULAR RISK STRATIFICATION IN PATIENTS WITH HYPERTENSION*

Major Risk Factors

- Smoking
- Dyslipidemia
- Diabetes mellitus
- Age older than 60 years
- Sex (men and postmenopausal women)
- Family history of cardiovascular disease: women under age 65 or men under age 55

Target Organ Damage/Clinical Cardiovascular Disease

- Heart diseases
  - Left ventricular hypertrophy
  - Angina/prior myocardial infarction
  - Prior coronary revascularization
  - Heart failure
- Stroke or transient ischemic attack
- Nephropathy
- Peripheral arterial disease
- Retinopathy

* See table 5.

Risk Stratification

The risk of cardiovascular disease in patients with hypertension is determined not only by the level of blood pressure but also by the presence or absence of target organ damage or other risk factors such as smoking, dyslipidemia, and diabetes, as shown in table 4. These factors independently modify the risk for subsequent cardiovascular disease, and their presence or absence is determined during the routine evaluation of patients with hypertension (i.e., history, physical examination, laboratory tests). Based on this assessment and the level of blood pressure, the patient's risk group can be determined, as shown in table 5. This empiric classification stratifies patients with hypertension into risk groups for therapeutic decisions. The World Health Organization Expert Committee on Hypertension Control recently recommended a similar approach.[62] Obesity and physical inactivity are also predictors of cardiovascular risk and interact with other risk factors, but they are of less significance in the selection of antihypertensive drugs.

Risk Group A

Risk group A includes patients with high-normal blood pressure or stage 1, 2, or 3 hypertension who do not have clinical cardiovascular disease, target organ damage, or other risk factors. Persons with stage 1 hypertension in risk group A are candidates for a longer trial (up to 1 year) of vigorous lifestyle modification with vigilant blood pressure monitoring. If goal blood pressure is not achieved, pharmacologic therapy should be added. For those with stage 2 or stage 3 hypertension, drug therapy is warranted.

Table 5

Risk Stratification and Treatment*

Blood Pressure Stages (mm Hg)	Risk Group A (No Risk Factors No TOD/CCD)†	Risk Group B (At Least 1 Risk Factor, Not Including Diabetes; No TOD/CCD)	Risk Group C (TOD/CCD and/or Diabetes, With or Without Other Risk Factors)
High-normal (130-139/85-89)	Lifestyle modification	Lifestyle modification	Drug therapy§
Stage 1 (140-159/90-99)	Lifestyle modification (up to 12 months)	Lifestyle modification‡ (up to 6 months)	Drug therapy
Stages 2 and 3 (≥160/≥100)	Drug therapy	Drug therapy	Drug therapy

For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as having stage 1 hypertension with target organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes). This patient would be categorized as Stage 1, Risk Group C, and recommended for immediate initiation of pharmacologic treatment.

* Lifestyle modification should be adjunctive therapy for all patients recommended for pharmacologic therapy.

† TOD/CCD indicates target organ disease/clinical cardiovascular disease (see table 4).

‡ For patients with multiple risk factors, clinicians should consider drugs as initial therapy plus lifestyle modifications.

§ For those with heart failure, renal insufficiency, or diabetes.

Risk Group B

Risk group B includes patients with hypertension who do not have clinical cardiovascular disease or target organ damage but have one or more of the risk factors shown in table 4 but not diabetes mellitus. This group contains the large majority of patients with high blood pressure. If multiple risk factors are present, clinicians should consider antihypertensive drugs as initial therapy. Lifestyle modification and management of reversible risk factors should be strongly recommended.

Risk Group C

Risk group C includes patients with hypertension who have clinically manifest cardiovascular disease or target organ damage, as delineated in table 4. It is the clinical opinion of the JNC VI executive committee that some patients who have high-normal blood pressure as well as renal insufficiency, heart failure, or diabetes mellitus should be considered for prompt pharmacologic therapy. Appropriate lifestyle modifications always should be recommended as adjunct treatment.

This classification (blood pressure stage and risk grouping) is directly linked to treatment and treatment goals as discussed in chapter 3. It provides practicing clinicians with a simple method of identifying risk strata for individual patients (by history, physical examination, and routine laboratory testing) as well as guidelines for treatment of those patients. From these findings, an assessment of absolute risk can be made. Tables, formulas, computer software programs, and World Wide Web sites are available for calculating cardiovascular risk in individual patients by means of data from epidemiologic studies.[63-66]

SUMMARY

- Table 2 provides a classification of blood pressure stages in adults. Stage 3 and stage 4 hypertension are now combined.
- Recommendations for detection, confirmation, and evaluation of high blood pressure remain consistent with those presented in the JNC V report.
- A new definition is proposed for normal blood pressure with self-monitoring and ambulatory blood pressure measurement.
- A discussion of genetics and a discussion of clinical clues to identifiable causes of hypertension have been added.
- New tables listing cardiovascular risk factors and describing risk stratification have been added.

CHAPTER 3

PREVENTION AND TREATMENT OF HIGH BLOOD PRESSURE

POTENTIAL FOR PRIMARY PREVENTION OF HYPERTENSION

Before considering the active treatment of established hypertension, the even greater need for prevention of disease should be recognized. Without primary prevention, the hypertension problem would never be solved and would rely solely on detection of existing high blood pressure. Primary prevention provides an attractive opportunity to interrupt and prevent the continuing costly cycle of managing hypertension and its complications. Primary prevention reflects a number of realities:

- A significant portion of cardiovascular disease occurs in people whose blood pressure is above the optimal level (120/80 mm Hg) but not so high as to be diagnosed or treated as hypertension.[40Pr,64F] A population-wide approach to lowering blood pressure can reduce this considerable burden of risk.
- Active treatment of established hypertension, as carefully as can be provided, poses financial costs and potential adverse effects.
- Most patients with established hypertension do not make sufficient lifestyle changes, do not take medication, or do not take enough medication to achieve control.[24X]
- Even if adequately treated according to current standards, patients with hypertension may not lower their risk to that of persons with normal blood pressure.[67F]
- Blood pressure rise and high blood pressure are not inevitable consequences of aging.[40F]

Therefore, an effective population-wide strategy to prevent blood pressure rise with age and to reduce overall blood pressure levels, even by a little, could affect overall cardiovascular morbidity and mortality as much as or more than that of treating only those with established disease.[29Pr]

Such a population-wide approach has been promulgated.[29Pr] It is based on lifestyle modifications that have been shown to prevent or delay the expected rise in blood pressure in susceptible people.[68Ra,69F,70Ra,71Ra,72Ra] A recent study demonstrated that a diet rich in fruits, vegetables, and low-fat dairy foods, and with reduced saturated and total fats, significantly lowers blood pressure[73Ra] (see appendix A).

Lifestyle modifications, discussed later in this chapter as being of value in the treatment of established hypertension, could have an even greater impact on disease prevention and should be recommended to the entire population. Modifications that do not require active participation of individuals but that can be provided to the entire population, such as a reduction in the amount of sodium chloride added to processed foods, may be even more effective.

GOAL

The goal of prevention and management of hypertension is to reduce morbidity and mortality by the least intrusive means possible. This may be accomplished by achieving and maintaining SBP *below* 140 mm Hg and DBP *below* 90 mm Hg and lower if tolerated,

while controlling other modifiable risk factors for cardiovascular disease. Treatment to lower levels may be useful, particularly to prevent stroke,[74Re] to preserve renal function,[75Ra] and to prevent or slow heart failure progression.[76F,77Ra] The goal may be achieved by lifestyle modification, alone or with pharmacologic treatment.

Lifestyle Modifications

Lifestyle modifications (table 6) offer the potential for preventing hypertension, have been shown to be effective in lowering blood pressure, and can reduce other cardiovascular risk factors at little cost and with minimal risk.[73Ra] Patients should be strongly encouraged to adopt these lifestyle modifications, particularly if they have additional risk factors for premature cardiovascular disease, such as dyslipidemia or diabetes mellitus. Even when lifestyle modifications alone are not adequate in controlling hypertension, they may reduce the number and dosage of antihypertensive medications needed to manage the condition.[77Ra,78C] Although the difficulty in achieving and maintaining lifestyle changes is recognized, a systematic team approach utilizing health care professionals and community resources when possible can assist in providing the necessary education, support, and followup.

Weight Reduction

Excess body weight—body mass index (weight in kilograms divided by height in meters, squared) of 27 or greater—is correlated closely with increased blood pressure. The deposition of excess fat in the upper part of the body (visceral or abdominal), as evidenced by a waist circumference of 34 inches (85 cm) or greater in women or 39 inches (98 cm) or greater in men, also has been associated with the risk for hypertension, dyslipidemia, diabetes, and coronary heart disease mortality.[79X]

Weight reduction, of as little as 10 pounds (4.5 kg) reduces blood pressure in a large proportion of overweight persons with hypertension.[72Ra,80Ra,81Pr] In overweight patients with hypertension, weight reduction enhances the blood-pressure-lowering effect of concurrent antihypertensive agents and can significantly reduce concomitant cardiovascular risk factors, such as diabetes and dyslipidemia.[77C]

Therefore, all patients with hypertension who are above their desirable weight should be placed on an individualized, monitored weight reduction program involving caloric restriction and increased physical activity. Recidivism is common and can be discouraging, but persis-

Table 6

Lifestyle Modifications for Hypertension Prevention and Management

- Lose weight if overweight.
- Limit alcohol intake to no more than 1 oz (30 mL) ethanol (e.g., 24 oz [720 mL] beer, 10 oz [300 mL] wine, or 2 oz [60 mL] 100-proof whiskey) per day or 0.5 oz (15 mL) ethanol per day for women and lighter weight people.
- Increase aerobic physical activity (30 to 45 minutes most days of the week).
- Reduce sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).
- Maintain adequate intake of dietary potassium (approximately 90 mmol per day).
- Maintain adequate intake of dietary calcium and magnesium for general health.
- Stop smoking and reduce intake of dietary saturated fat and cholesterol for overall cardiovascular health.

tence may be rewarded by reduction of multiple cardiovascular risk factors and a step-down in antihypertensive drug therapy. Anorectic agents should be used with caution because many can raise blood pressure and some may increase the risk for valvular heart disease[82] and pulmonary hypertension.[83Re]

Moderation of Alcohol Intake

Excessive alcohol intake is an important risk factor for high blood pressure,[69F] can cause resistance to antihypertensive therapy,[84Ra] and is a risk factor for stroke.[85Re] A detailed history of current alcohol consumption should be elicited from patients. Those who drink beverages containing alcohol should be counseled to limit their daily intake to no more than 1 ounce (30 mL) of ethanol—for example, 24 ounces (720 mL) of beer, 10 ounces (300 mL) of wine, or 2 ounces (60 mL) of 100-proof whiskey. Because women absorb more ethanol than men[86C] and lighter weight people are more susceptible than heavier people to the effects of alcohol, these groups should be counseled to limit their intake to no more than 0.5 ounce (15 mL) of ethanol per day.[87] Such amounts do not raise blood pressure and have been associated with a lower risk for CHD. Significant hypertension may develop during abrupt withdrawal from heavy alcohol consumption but recedes a few days after alcohol consumption is reduced.

Physical Activity

Regular aerobic physical activity—adequate to achieve at least a moderate level of physical fitness—can enhance weight loss and functional health status and reduce the risk for cardiovascular disease and all-cause mortality.[88F,89Ra] When compared with their more active and fit peers, sedentary individuals with normal blood pressure have a 20- to 50-percent increased risk of developing hypertension.[90F]

Blood pressure can be lowered with moderately intense physical activity (40 to 60 percent of maximum oxygen consumption), such as 30 to 45 minutes of brisk walking most days of the week.[81Pr] Most people can safely increase their level of physical activity without an extensive medical evaluation. Patients with cardiac or other serious health problems need a more thorough evaluation, often including a cardiac stress test, and may need referral to a specialist or medically supervised exercise program.

Moderation of Dietary Sodium

Sodium, in the form of sodium chloride or table salt, is linked to levels of blood pressure. Individual response of blood pressure to variation in sodium intake differs widely; as groups, African Americans, older people, and patients with hypertension or diabetes are more sensitive to changes in dietary sodium chloride than are others in the general population.[91Pr]

Epidemiologic data demonstrate a positive association between sodium intake and level of blood pressure.[92X] Meta-analysis of clinical trials reveals that a reduction of 75 to 100 mmol in sodium intake lowers blood pressure over periods of several weeks to a few years.[93M] These effects are greater for older persons and those with elevated pressures.[93M,94M] An analysis of 17 published randomized controlled trials involving patients age 45 or older with hypertension found an average decrease of 6.3/2.2 mm Hg with a urinary sodium reduction of 95 mmol per day.[94M] Although concern about severe sodium restriction has been raised in one observational study,[95F] there is no evidence that lower levels of sodium intake, as achieved in intervention trials, present any safety hazards.

Moreover, a variety of controlled and observational studies suggest that a diet with moderately reduced intake of sodium may be associated with other favorable effects on factors such as ability to reduce the need for antihypertensive medication, reduce diuretic-induced potassium wastage, possibly regress left ventricular hypertrophy, and protect from osteoporosis and renal stones through reduction in urinary calcium excretion.[77C,78Ra,96F,97Ra,98Pr,99F,100Ra,101Pr]

Seventy-five percent of sodium intake is derived from processed food. Because the average American consumption of sodium is in excess of 150 mmol per day, moderate sodium reduction to a level of no more than 100 mmol per day (approximately 6 grams of sodium chloride or 2.4 grams of sodium per day) is recommended and achievable. With appropriate counseling, patients and their families can learn to read food labels and select foods lower in sodium.[87] Such items are becoming more readily available in supermarkets and restaurants.

Potassium Intake

High dietary potassium intake may protect against developing hypertension and improve blood pressure control in patients with hypertension.[102M] Inadequate potassium intake may increase blood pressure.[69F] Therefore, an adequate intake of potassium (approximately 90 mmol per day), preferably from food sources such as fresh fruits and vegetables,[73Ra] should be maintained. If hypokalemia occurs during diuretic therapy, additional potassium may be needed from potassium-containing salt substitutes, potassium supplements, or potassium-sparing diuretics. These agents must be used with caution in patients susceptible to hyperkalemia, including those with renal insufficiency or those receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers.

Calcium Intake

In most epidemiologic studies, low dietary calcium intake is associated with an increased prevalence of hypertension.[103F] An increased calcium intake may lower blood pressure in some patients with hypertension, but the overall effect is minimal.[104M] Although it is important to maintain an adequate intake of calcium for general health, there is currently no rationale for recommending calcium supplements to lower blood pressure.

Magnesium Intake

Although evidence suggests an association between lower dietary magnesium intake and higher blood pressure,[69F] no convincing data currently justify recommending an increased magnesium intake in an effort to lower blood pressure.

Other Dietary Factors

Dietary Fats. Dyslipidemia is a major independent risk factor for coronary artery disease; therefore, dietary therapy and, if necessary, drug therapy for dyslipidemia are an important adjunct to antihypertensive treatment. In randomized controlled studies, diets varying in total fat and proportions of saturated to unsaturated fats have had little, if any, effect on blood pressure. Large amounts of omega-3 fatty acids may lower blood pressure; however, some patients experience abdominal discomfort.[105Ra] One study found no significant effect in preventing hypertension.[71Ra]

Caffeine. Caffeine may raise blood pressure acutely. Tolerance to this pressor effect develops rapidly, and no direct relationship between caffeine intake and elevated blood pressure has been found in most epidemiologic surveys.[69F]

Other Factors. Although recent epidemiologic studies have shown an inverse relationship between dietary protein to blood pressure, no consistent effects have been demonstrated.[106Pr,107F] Furthermore, controlled trials of varying proportions of carbohydrate, garlic, or onion in the diet have demonstrated no consistent effects on blood pressure.

Relaxation and Biofeedback

Emotional stress can raise blood pressure acutely. The role of stress management techniques in treating patients with elevated blood pressure is uncertain. Relaxation therapies and biofeedback have been studied in multiple controlled trials with little effect beyond that seen in the control groups.[108Ra] A study in African Americans showed significant decreases in SBP and DBP at 3 months.[109Ra] However, the available literature

does not support the use of relaxation therapies for definitive therapy or prevention of hypertension. One study found no effect of stress management on prevention of hypertension.[71Ra]

Tobacco Avoidance for Overall Cardiovascular Risk Reduction

Cigarette smoking is a powerful risk factor for cardiovascular disease, and avoidance of tobacco in any form is essential. A significant rise in blood pressure accompanies the smoking of each cigarette. Those who continue to smoke may not receive the full degree of protection against cardiovascular disease from antihypertensive therapy.[110F] The cardiovascular benefits of discontinuing tobacco use can be seen within a year in all age groups.[111Pr] Smoking cessation information is available from voluntary health organizations and Federal agencies.[112-115] Smokers must be told repeatedly and unambiguously to stop smoking. The lower amounts of nicotine contained in smoking cessation aids usually will not raise blood pressure; therefore, they may be used with appropriate counseling and behavior interventions.[116Re] Actions to avoid or minimize weight gain after quitting smoking are often needed.[117F]

Implementation of lifestyle modifications should not delay the start of an effective antihypertensive drug regimen in those at higher risk (table 5).

Pharmacologic Treatment

The decision to initiate pharmacologic treatment requires consideration of several factors: the degree of blood pressure elevation, the presence of target organ damage, and the presence of clinical cardiovascular disease or other risk factors (tables 4 and 5).

Efficacy

Reducing blood pressure with drugs clearly decreases cardiovascular morbidity and mortality. Protection has been demonstrated for stroke, coronary events, heart failure, progression of renal disease, progression to more severe hypertension, and all-cause mortality[118M,119Pr] (figure 6).

Among older persons, treatment of hypertension has been associated with an even more significant reduction in CHD[120M] (figure 7).

These results have been obtained in patients in various countries regardless of sex, age, race, blood pressure level, or socioeconomic status. Therefore, these findings can be generalized with confidence to the entire adult population with high blood pressure.

Drug Therapy Considerations

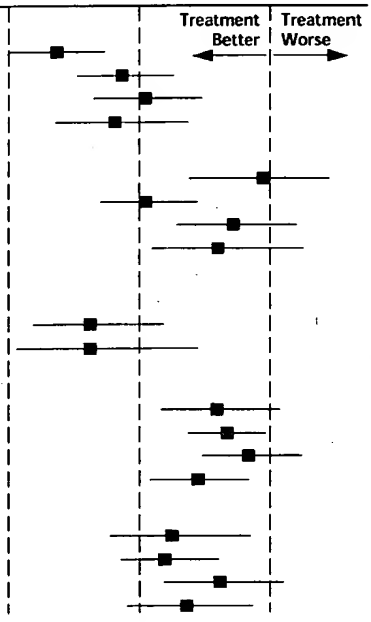
Most antihypertensive drugs currently available in the United States are listed in tables 7 and 8. For most patients, a low dose of the initial drug choice should be used, slowly titrating upward at a schedule dependent on the patient's age, needs, and responses. The optimal formulation should provide 24-hour efficacy with a once-daily dose, with at least 50 percent of the peak effect remaining at the end of the 24 hours. Long-acting formulations that provide 24-hour efficacy are preferred over short-acting agents for many reasons: (1) adherence is better with once-daily dosing; (2) for some agents, fewer tablets incur lower cost; (3) control of hypertension is persistent and smooth rather than intermittent; and (4) protection is provided against whatever risk for sudden death, heart attack, and stroke that is due to the abrupt increase of blood pressure after arising from overnight sleep. Agents with a duration of action beyond 24 hours are attractive because many patients inadvertently miss at least one dose of medication each week. Nonetheless, twice-daily dosing may offer similar control at possibly lower cost.

Newly developed formulations provide additional medication choices. For example, combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent adverse effects (table 8). Very low doses of a diuretic (e.g., 6.25 mg of hydrochlorothiazide) can potentiate the effect of the other agent without producing adverse metabolic effects.[121Ra] Low-dose combinations with an

Figure 6

META-ANALYSIS OF RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIALS IN HYPERTENSION ACCORDING TO FIRST-LINE TREATMENT STRATEGY

Outcome / Drug Regimen	Dose	No. of Trials	Events, Active Treatment/ Control	RR (95% CI)
Stroke				
Diuretics	High	9	88/232	0.49 (0.39-0.62)
Diuretics	Low	4	191/347	0.66 (0.55-0.78)
Beta-blockers		4	147/335	0.71 (0.59-0.86)
HDFP	High	1	102/158	0.64 (0.50-0.82)
Coronary Heart Disease				
Diuretics	High	11	211/331	0.99 (0.83-1.18)
Diuretics	Low	4	215/363	0.72 (0.61-0.85)
Beta-blockers		4	243/459	0.93 (0.80-1.09)
HDFP	High	1	171/189	0.90 (0.73-1.10)
Congestive Heart Failure				
Diuretics	High	9	6/35	0.17 (0.07-0.41)
Diuretics	Low	3	81/134	0.58 (0.44-0.76)
Beta-blockers		2	41/175	0.58 (0.40-0.84)
Total Mortality				
Diuretics	High	11	224/382	0.88 (0.75-1.03)
Diuretics	Low	4	514/713	0.90 (0.81-0.99)
Beta-blockers		4	383/700	0.95 (0.84-1.07)
HDFP	High	1	349/419	0.83 (0.72-0.95)
Cardiovascular Mortality				
Diuretics	High	11	124/230	0.78 (0.62-0.97)
Diuretics	Low	4	237/390	0.76 (0.65-0.89)
Beta-blockers		4	214/410	0.89 (0.76-1.05)
HDFP	High	1	195/240	0.81 (0.67-0.97)

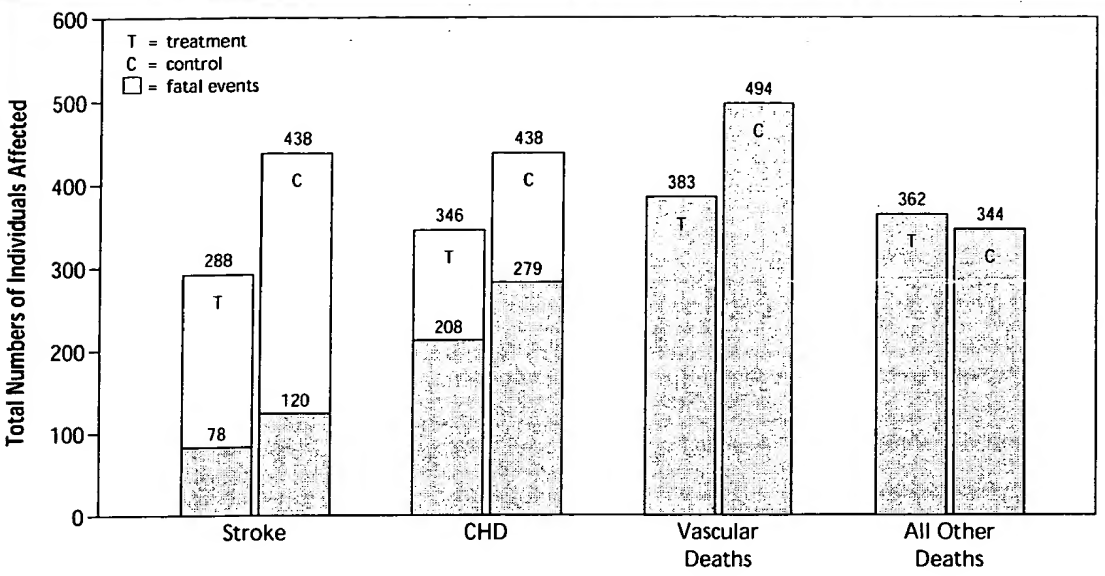


Trials indicate number of trials with at least one endpoint of interest. For these comparisons, the numbers of participants randomized to active therapy and placebo, respectively, were 7,768 and 12,075 for high-dose diuretic therapy; 4,305 and 5,116 for low-dose diuretic therapy, and 6,736 and 12,147 for beta-blocker therapy. Because the Medical Research Council trials included two active arms, the placebo group is included twice in these totals (for diuretic comparison and for beta-blocker comparison). The total number of participants randomized to active therapy and control therapy were 24,294 and 23,926, respectively. RR indicates relative risk; CI, confidence interval; and HDFP, Hypertension Detection and Follow-up Program (5,484 subjects in stepped care and 5,455 in referred care).

Source: Psaty et al.[118]

Figure 7

Combined Results of Five Randomized Trials of Antihypertensive Treatment in the Elderly



	Stroke	CHD	Vascular Deaths	All Other Deaths
% (SD) reduction in odds	34% (6) 2P <0.0001	19% (7) 2P <0.05	23% (6) 2P <0.001	-7% (8) 2P >0.5

The studies assessed the effects of blood pressure reduction on stroke, coronary heart disease, vascular death, and nonvascular death in a total of 12,483 patients over age 60 (SBP difference of 12-14 mm Hg, DBP difference of 5-6 mm Hg), followup 5 years.

SD = standard deviation

Source: Reprinted from MacMahon and Rodgers[120] by courtesy of Marcel Dekker, Inc.

Table 7

ORAL ANTIHYPERTENSIVE DRUGS*

Drug	Trade Name	Usual Dose Range, Total mg/day* (Frequency per Day)	Selected Side Effects and Comments*
Diuretics (partial list)			Short-term: increases cholesterol and glucose levels; biochemical abnormalities: decreases potassium, sodium, and magnesium levels, increases uric acid and calcium levels; rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia
Chlorthalidone (G)†	Hygroton	12.5-50 (1)	
Hydrochlorothiazide (G)	Hydrodiuril, Microzide, Esidrix	12.5-50 (1)	
Indapamide	Lozol	1.25-5 (1)	(Less or no hypercholesterolemia)
Metolazone	Mykrox	0.5-1.0 (1)	
	Zaroxolyn	2.5-10 (1)	
Loop diuretics			
Bumetanide (G)	Bumex	0.5-4 (2-3)	(Short duration of action, no hypercalcemia)
Ethacrynic acid	Edecrin	25-100 (2-3)	(Only nonsulfonamide diuretic, ototoxicity)
Furosemide (G)	Lasix	40-240 (2-3)	(Short duration of action, no hypercalcemia)
Torsemide	Demadex	5-100 (1-2)	
Potassium-sparing agents			Hyperkalemia
Amiloride hydrochloride (G)	Midamor	5-10 (1)	
Spironolactone (G)	Aldactone	25-100 (1)	(Gynecomastia)
Triamterene (G)	Dyrenium	25-100 (1)	
Adrenergic inhibitors			
Peripheral agents			
Guanadrel	Hylorel	10-75 (2)	(Postural hypotension, diarrhea)
Guanethidine monosulfate	Ismelin	10-150 (1)	(Postural hypotension, diarrhea)
Reserpine (G)**	Serpasil	0.05-0.25 (1)	(Nasal congestion, sedation, depression, activation of peptic ulcer)
Central alpha-agonists			Sedation, dry mouth, bradycardia,withdrawal hypertension
Clonidine hydrochloride (G)	Catapres	0.2-1.2 (2-3)	(More withdrawal)
Guanabenz acetate (G)	Wytensin	8-32 (2)	
Guanfacine hydrochloride (G)	Tenex	1-3 (1)	(Less withdrawal)
Methyldopa (G)	Aldomet	500-3,000 (2)	(Hepatic and "autoimmune" disorders)
Alpha-blockers			Postural hypotension
Doxazosin mesylate	Cardura	1-16 (1)	
Prazosin hydrochloride (G)	Minipress	2-30 (2-3)	
Terazosin hydrochloride	Hytrin	1-20 (1)	
Beta-blockers			Bronchospasm, bradycardia, heart failure, may mask insulin-induced hypoglycemia; less serious: impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity)
Acebutolol§‡	Sectral	200-800 (1)	
Atenolol (G)§	Tenormin	25-100 (1-2)	
Betaxolol§	Kerlone	5-20 (1)	
Bisoprolol fumarate§	Zebeta	2.5-10 (1)	
Carteolol hydrochloride‡	Cartrol	2.5-10 (1)	
Metoprolol tartrate (G)§	Lopressor	50-300 (2)	
Metoprolol succinate§	Toprol-XL	50-300 (1)	
Nadolol (G)	Corgard	40-320 (1)	
Penbutolol sulfate‡	Levatol	10-20 (1)	
Pindolol (G)‡	Visken	10-60 (2)	
Propranolol hydrochloride (G)	Inderal	40-480 (2)	
	Inderal LA	40-480 (1)	
Timolol maleate (G)	Blocadren	20-60 (2)	

Table 7

ORAL ANTIHYPERTENSIVE DRUGS* (CONTINUED)

Drug	Trade Name	Usual Dose Range, Total mg/day* (Frequency per Day)	Selected Side Effects and Comments*
Combined alpha- and beta-blockers			Postural hypotension, bronchospasm
Carvedilol	Coreg	12.5-50 (2)	
Labetalol hydrochloride (G)	Normodyne, Trandate	200-1,200 (2)	
Direct vasodilators			Headaches, fluid retention, tachycardia
Hydralazine hydrochloride (G)	Apresoline	50-300 (2)	(Lupus syndrome)
Minoxidil (G)	Loniten	5-100 (1)	(Hirsutism)
Calcium antagonists			
Nondihydropyridines			Conduction defects, worsening of systolic dysfunction, gingival hyperplasia
Diltiazem hydrochloride	Cardizem SR	120-360 (2)	(Nausea, headache)
	Cardizem CD, Dilacor XR, Tiazac	120-360 (1)	
Mibefradil dihydrochloride (T-channel calcium antagonist)	Posicor	50-100 (1)	(No worsening of systolic dysfunction; contraindicated with terfenadine [Seldane], astemizole [Hismanal], and cisapride [Propulsid])
Verapamil hydrochloride	Isoptin SR, Calan SR	90-480 (2)	(Constipation)
	Verelan, Covera HS	120-480 (1)	
Dihydropyridines			Edema of the ankle, flushing, headache, gingival hypertrophy
Amlodipine besylate	Norvasc	2.5-10 (1)	
Felodipine	Plendil	2.5-20 (1)	
Isradipine	DynaCirc	5-20 (2)	
	DynaCirc CR	5-20 (1)	
Nicardipine	Cardene SR	60-90 (2)	
Nifedipine	Procardia XL, Adalat CC	30-120 (1)	
Nisoldipine	Sular	20-60 (1)	
ACE inhibitors			Common: cough; rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia
Benazepril hydrochloride	Lotensin	5-40 (1-2)	
Captopril (G)	Capoten	25-150 (2-3)	
Enalapril maleate	Vasotec	5-40 (1-2)	
Fosinopril sodium	Monopril	10-40 (1-2)	
Lisinopril	Prinivil, Zestril	5-40 (1)	
Moexipril	Univasc	7.5-15 (1-2)	
Quinapril hydrochloride	Accupril	5-80 (1-2)	
Ramipril	Altace	1.25-20 (1-2)	
Trandolapril	Mavik	1-4 (1)	
Angiotensin II receptor blockers			Angioedema (very rare), hyperkalemia
Losartan potassium	Cozaar	25-100 (1-2)	
Valsartan	Diovan	80-320 (1)	
Irbesartan	Avapro	150-300 (1)	

* These dosages may vary from those listed in the *Physicians' Desk Reference* (51st edition), which may be consulted for additional information. The listing of side effects is not all-inclusive, and side effects are for the class of drugs except where noted for individual drugs (in parentheses); clinicians are urged to refer to the package insert for a more detailed listing.

† (G) indicates generic available.

‡ Has intrinsic sympathomimetic activity.

§ Cardioselective.

**Also acts centrally.

Table 8

Combination Drugs for Hypertension

Drug	Trade Name
Beta-adrenergic blockers and diuretics	
Atenolol, 50 or 100 mg/chlorthalidone, 25 mg	Tenoretic
Bisoprolol fumarate, 2.5, 5, or 10 mg/hydrochlorothiazide, 6.25 mg	Ziac*
Metoprolol tartrate, 50 or 100 mg/hydrochlorothiazide, 25 or 50 mg	Lopressor HCT
Nadolol, 40 or 80 mg/bendroflumethiazide, 5 mg	Corzide
Propranolol hydrochloride, 40 or 80 mg/hydrochlorothiazide, 25 mg	Inderide
Propranolol hydrochloride (extended release), 80, 120, or 160 mg/hydrochlorothiazide, 50 mg	Inderide LA
Timolol maleate, 10 mg/hydrochlorothiazide, 25 mg	Timolide
ACE inhibitors and diuretics	
Benazepril hydrochloride, 5, 10, or 20 mg/hydrochlorothiazide, 6.25, 12.5, or 25 mg	Lotensin HCT
Captopril, 25 or 50 mg/hydrochlorothiazide, 15 or 25 mg	Capozide*
Enalapril maleate, 5 or 10 mg/hydrochlorothiazide, 12.5 or 25 mg	Vaseretic
Lisinopril, 10 or 20 mg/hydrochlorothiazide, 12.5 or 25 mg	Prinzide, Zestoretic
Angiotensin II receptor antagonists and diuretics	
Losartan potassium, 50 mg/hydrochlorothiazide, 12.5 mg	Hyzaar
Calcium antagonists and ACE inhibitors	
Amlodipine besylate, 2.5 or 5 mg/benazepril hydrochloride, 10 or 20 mg	Lotrel
Diltiazem hydrochloride, 180 mg/enalapril maleate, 5 mg	Teczem
Verapamil hydrochloride (extended release), 180 or 240 mg/trandolapril, 1, 2, or 4 mg	Tarka
Felodipine, 5 mg/enalapril maleate, 5 mg	Lexxel
Other combinations	
Triamterene, 37.5, 50, or 75 mg/hydrochlorothiazide, 25 or 50 mg	Dyazide, Maxide
Spironolactone, 25 or 50 mg/hydrochlorothiazide, 25 or 50 mg	Aldactazide
Amiloride hydrochloride, 5 mg/hydrochlorothiazide, 50 mg	Moduretic
Guanethidine monosulfate, 10 mg/hydrochlorothiazide, 25 mg	Esimil
Hydralazine hydrochloride, 25, 50, or 100 mg/hydrochlorothiazide, 25 or 50 mg	Apresazide
Methyldopa, 250 or 500 mg/hydrochlorothiazide, 15, 25, 30, or 50 mg	Aldoril
Reserpine, 0.125 mg/hydrochlorothiazide, 25 or 50 mg	Hydropres
Reserpine, 0.10 mg/hydralazine hydrochloride, 25 mg/hydrochlorothiazide, 15 mg	Ser-Ap-Es
Clonidine hydrochloride, 0.1, 0.2, or 0.3 mg/chlorthalidone, 15 mg	Combipres
Methyldopa, 250 mg/chlorothiazide, 150 or 250 mg	Aldochlor
Reserpine, 0.125 or 0.25 mg/chlorthalidone, 25 or 50 mg	Demi-Regroton
Reserpine, 0.125 or 0.25 mg/chlorothiazide, 250 or 500 mg	Diupres
Prazosin hydrochloride, 1, 2, or 5 mg/polythiazide, 0.5 mg	Minizide

*Approved for initial therapy.

ACE inhibitor and a nondihydropyridine calcium antagonist may reduce proteinuria more than either drug alone.[122Pr] Combinations of a dihydropyridine calcium antagonist and an ACE inhibitor induce less pedal edema than does the calcium antagonist alone.[123Ra] In some instances, drugs with similar modes of action may provide additive effects, such as metolazone and a loop diuretic in renal failure.

ACE inhibitors have been shown to provide beneficial effects in a variety of hypertension-related processes including heart failure from systolic dysfunction and nephropathy (see chapter 4). The recently introduced angiotensin II receptor blockers produce hemodynamic effects similar to those of ACE inhibitors while avoiding the most common adverse effect, dry cough. However, in the absence of data documenting equal long-term cardiac and renal protection in patients with these conditions, angiotensin II receptor blockers should be used primarily in patients in whom ACE inhibitors are indicated but who are unable to tolerate them.

Some antihypertensive agents—such as direct-acting smooth-muscle vasodilators, central alpha$_2$-agonists, and peripheral adrenergic antagonists—are not well suited for initial monotherapy because they produce annoying adverse effects in many patients. Reserpine has a uniquely prolonged therapeutic effect and is better tolerated in low doses (0.05 to 0.10 mg per day); however, patients and their families still should be warned about the possibility of depression. The direct-acting smooth-muscle vasodilators (e.g., hydralazine hydrochloride, minoxidil) often induce reflex sympathetic stimulation of the cardiovascular system and fluid retention.

Immediate-release nifedipine has precipitated ischemic events[124Pr] and, in large doses, may increase coronary mortality in patients who have had a myocardial infarction.[125M] Therefore, this agent should be used only with great caution, if at all. There have been inconsistent reports regarding adverse health effects of short-acting or immediate-release formulations of nifedipine, diltiazem hydrochloride, and verapamil hydrochloride.[126Pr,127] Randomized controlled trials are now in progress with long-acting types and formulations of calcium antagonists approved for treatment of hypertension. In the meantime, specific recommendations are provided in tables 9 and 10 and figure 8.

Special Considerations

Special considerations in the selection of initial therapy include demographic characteristics, concomitant diseases that may be beneficially or adversely affected by the antihypertensive agent chosen (table 9), quality of life, cost, and use of other drugs that may lead to drug interactions (table 11). When choosing a certain drug for its favorable effect on comorbidity, clinicians should be aware that reduction of long-term cardiovascular morbidity and mortality may not have been demonstrated.[118M]

Demographics. Neither sex nor age usually affects responsiveness to various agents.[128M] In general, hypertension in African Americans is more responsive to monotherapy with diuretics and calcium antagonists than to beta-blockers or ACE inhibitors.[129Ra] However, if a beta-blocker or ACE inhibitor is needed for other therapeutic benefits, differences in efficacy usually can be overcome with reduction of salt intake, higher doses of the drug, or addition of a diuretic.

Concomitant Diseases and Therapies. Antihypertensive drugs may worsen some diseases and improve others (table 9). Selection of an antihypertensive agent that also treats a coexisting disease will simplify therapeutic regimens and reduce costs.

Quality of Life. Although antihypertensive drugs may cause adverse effects in some patients (table 7), quality of life is maintained and possibly improved by any of the agents recommended for initial therapy.[130Ra]

Table 9

Considerations for Individualizing Antihypertensive Drug Therapy*

Indication	Drug Therapy
Compelling Indications Unless Contraindicated	
Diabetes mellitus (type 1) with proteinuria	ACE I
Heart failure	ACE I, diuretics
Isolated systolic hypertension (older patients)	Diuretics (preferred), CA (long-acting DHP)
Myocardial infarction	Beta-blockers (non-ISA), ACE I (with systolic dysfunction)
May Have Favorable Effects on Comorbid Conditions†	
Angina	Beta-blockers, CA
Atrial tachycardia and fibrillation	Beta-blockers, CA (non-DHP)
Cyclosporine-induced hypertension (caution with the dose of cyclosporine)	CA
Diabetes mellitus (types 1 and 2) with proteinuria	ACE I (preferred), CA
Diabetes mellitus (type 2)	Low-dose diuretics
Dyslipidemia	Alpha-blockers
Essential tremor	Beta-blockers (non-CS)
Heart failure	Carvedilol, losartan potassium
Hyperthyroidism	Beta-blockers
Migraine	Beta-blockers (non-CS), CA (non-DHP)
Myocardial infarction	Diltiazem hydrochloride, verapamil hydrochloride
Osteoporosis	Thiazides
Preoperative hypertension	Beta-blockers
Prostatism (BPH)	Alpha-blockers
Renal insufficiency (caution in renovascular hypertension and creatinine $\geq$265.2 µmol/L [3 mg/dL])	ACE I
May Have Unfavorable Effects on Comorbid Conditions†‡	
Bronchospastic disease	Beta-blockers§
Depression	Beta-blockers, central alpha-agonists, reserpine§
Diabetes mellitus (types 1 and 2)	Beta-blockers, high-dose diuretics
Dyslipidemia	Beta-blockers (non-ISA), diuretics (high-dose)
Gout	Diuretics
2° or 3° heart block	Beta-blockers,§ CA (non-DHP)§
Heart failure	Beta-blockers (except carvedilol), CA (except amlodipine besylate, felodipine)
Liver disease	Labetalol hydrochloride, methyldopa§
Peripheral vascular disease	Beta-blockers
Pregnancy	ACE I,§ angiotensin II receptor blockers§
Renal insufficiency	Potassium-sparing agents
Renovascular disease	ACE I, angiotensin II receptor blockers

* For initial drug therapy recommendations, see figure 8. For references, see chapter 4, *Physicians' Desk Reference* (51st edition), and Kaplan and Gifford.[134] ACE I indicates angiotensin-converting enzyme inhibitors; BPH, benign prostatic hyperplasia; CA, calcium antagonists; DHP, dihydropyridine; ISA, intrinsic sympathomimetic activity; MI, myocardial infarction; and non-CS, noncardioselective.

† Conditions and drugs are listed in alphabetical order.

‡ These drugs may be used with special monitoring unless contraindicated.

§ Contraindicated.

Table 10

PARENTERAL DRUGS FOR TREATMENT OF HYPERTENSIVE EMERGENCIES*

Drug	Dose†	Onset of Action	Duration of Action	Adverse Effects‡	Special Indications
Vasodilators					
Sodium nitroprusside	0.25-10 µg/kg per min as IV infusion§ (maximal dose for 10 min only)	Immediate	1-2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5-15 mg/h IV	5-10 min	1-4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1-0.3 µg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5-100 µg/min as IV infusion§	2-5 min	3-5 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25-5 mg every 6 h IV	15-30 min	6 h	Precipitous fall in pressure in high-renin states; response variable	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10-20 mg IV 10-50 mg IM	10-20 min 20-30 min	3-8 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Diazoxide	50-100 mg IV bolus repeated, or 15-30 mg/min infusion	2-4 min	6-12 h	Nausea, flushing, tachycardia, chest pain	Now obsolete; when no intensive monitoring available
Adrenergic inhibitors					
Labetalol hydrochloride	20-80 mg IV bolus every 10 min 0.5-2.0 mg/min IV infusion	5-10 min	3-6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250-500 µg/kg/min for 1 min, then 50-100 µg/kg/min for 4 min; may repeat sequence	1-2 min	10-20 min	Hypotension, nausea	Aortic dissection, perioperative
Phentolamine	5-15 mg IV	1-2 min	3-10 min	Tachycardia, flushing, headache	Catecholamine excess

* These doses may vary from those in the *Physicians' Desk Reference* (51st edition).

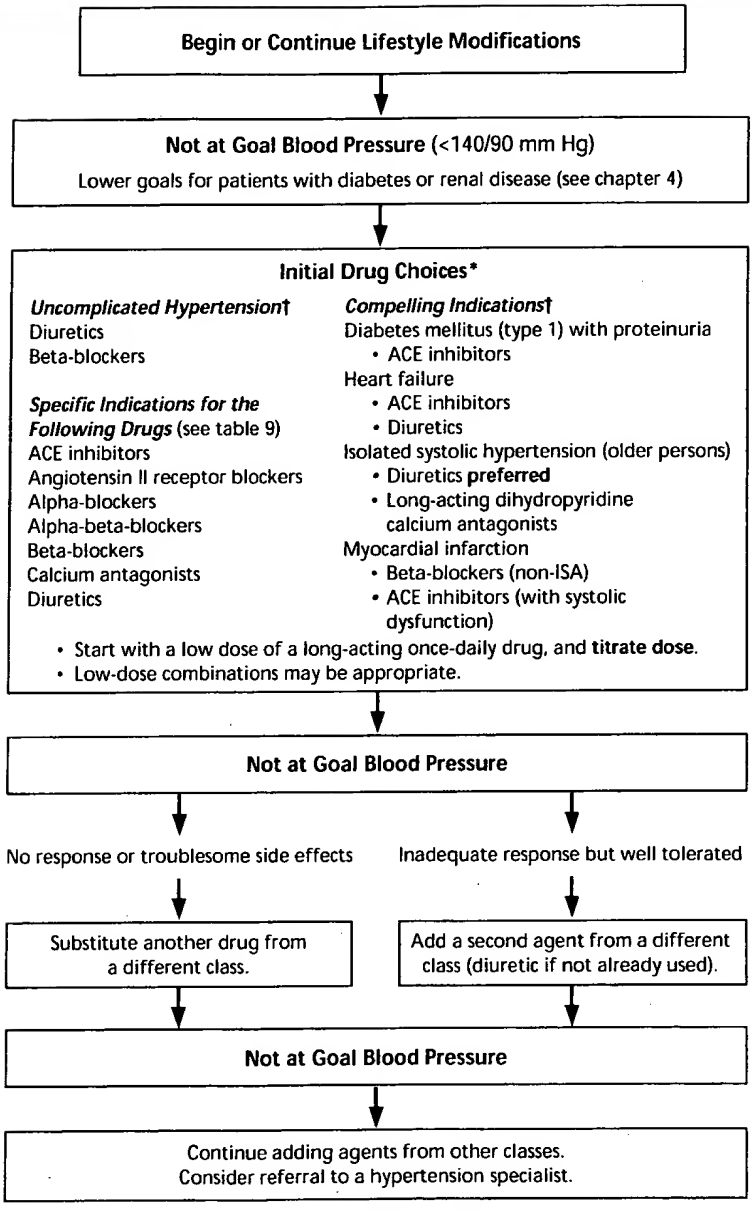
† IV indicates intravenous; IM, intramuscular.

‡ Hypotension may occur with all agents.

§ Require special delivery system.

Figure 8

ALGORITHM FOR THE TREATMENT OF HYPERTENSION



* Unless contraindicated. ACE indicates angiotensin-converting enzyme; ISA, intrinsic sympathomimetic activity.

† Based on randomized controlled trials (see chapters 3 and 4).

Table 11

Selected Drug Interactions With Antihypertensive Therapy*

Class of Agent	Increase Efficacy	Decrease Efficacy	Effect on Other Drugs
Diuretics	• Diuretics that act at different sites in the nephron (e.g., furosemide + thiazides)	• Resin-binding agents • NSAIDs • Steroids	• Diuretics raise serum lithium levels. • Potassium-sparing agents may exacerbate hyperkalemia due to ACE inhibitors.
Beta-blockers	• Cimetidine (hepatically metabolized beta-blockers) • Quinidine (hepatically metabolized beta-blockers) • Food (hepatically metabolized beta-blockers)	• NSAIDs • Withdrawal of clonidine • Agents that induce hepatic enzymes, including rifampin and phenobarbital	• Propranolol hydrochloride induces hepatic enzymes to increase clearance of drugs with similar metabolic pathways. • Beta-blockers may mask and prolong insulin-induced hypoglycemia. • Heart block may occur with nondihydropyridine calcium antagonists. • Sympathomimetics cause unopposed alpha-adrenoceptor-mediated vasoconstriction. • Beta-blockers increase angina-inducing potential of cocaine.
ACE inhibitors	• Chlorpromazine or clozapine	• NSAIDs • Antacids • Food decreases absorption (moexipril)	• ACE inhibitors may raise serum lithium levels. • ACE inhibitors may exacerbate hyperkalemic effect of potassium-sparing diuretics.
Calcium antagonists	• Grapefruit juice (some dihydropyridines) • Cimetidine or ranitidine (hepatically metabolized calcium antagonists)	• Agents that induce hepatic enzymes, including rifampin and phenobarbital	• Cyclosporine levels increase† with diltiazem hydrochloride, verapamil hydrochloride, mibefradil dihydrochloride, or nicardipine hydrochloride (but not felodipine, isradipine, or nifedipine). • Nondihydropyridines increase levels of other drugs metabolized by the same hepatic enzyme system, including digoxin, quinidine, sulfonylureas, and theophylline. • Verapamil hydrochloride may lower serum lithium levels. • Prazosin may decrease clearance of verapamil hydrochloride.
Alpha-blockers			
Central alpha$_2$-agonists and peripheral neuronal blockers		• Tricyclic antidepressants (and probably phenothiazines) • Monoamine oxidase inhibitors • Sympathomimetics or phenothiazines antagonize guanethidine monosulfate or guanadrel sulfate • Iron salts may reduce methyldopa absorption	• Methyldopa may increase serum lithium levels. • Severity of clonidine hydrochloride withdrawal may be increased by beta-blockers. • Many agents used in anesthesia are potentiated by clonidine hydrochloride.

* For initial drug therapy recommendations, see figure 8. See also *Physicians' Desk Reference* (51st edition) and *Cardiovascular Pharmacotherapeutics* (New York: McGraw Hill), 1997. NSAIDs indicate nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme.

† This is a clinically and economically beneficial drug-drug interaction because it both retards progression of accelerated atherosclerosis in heart transplant recipients and reduces the required daily dose of cyclosporine.

Physiological and Biochemical Measurements. Some clinicians have found certain physiological and biochemical measurements (e.g., body weight, heart rate, plasma renin activity, hemodynamic measurements) to be helpful in choosing specific therapy.

Economic Considerations. The cost of therapy may be a barrier to controlling high blood pressure and should be an important consideration in selecting antihypertensive medication. Generic formulations are acceptable. Nongeneric newer drugs are usually more expensive than diuretics or beta-blockers. If newer agents eventually prove to be equally effective, then cost should be considered in choosing them for initial therapy; if they prove to be more effective, then cost should be a secondary consideration. Treatment costs include not only the price of drugs but also the expense of routine or special laboratory tests, supplemental therapies, office visits, and time lost from work for visits to physicians' offices. The costs of medications may be reduced by using combination tablets and generic formulations. Patients should be advised to check prices at different sources. Some larger tablets can be divided, saving money when larger doses cost little more than smaller doses. Some sustained-release formulations should not be divided because cutting the tablet eliminates the sustained-release function.

Managed Care. Because high blood pressure is so common, its management requires a major commitment from clinicians and managed care organizations. This commitment will need to expand even further because the majority of patients with hypertension do not have adequately controlled blood pressure (see chapter 1) and additional demands will develop from the projected increase in numbers of persons with hypertension due to the aging of the population. However, the cost of managing hypertension is lower overall than the sum of direct and indirect costs that may be avoided by reducing hypertension-associated heart disease, stroke, and renal failure, especially because these adverse events often lead to expensive hospitalizations, surgical procedures, and high-cost technologies.[131Pr,132Pr,133Pr] Randomized controlled trials have demonstrated that these reductions occur in a relatively short time and are sustained for years.

Managed care programs offer the opportunity for a coordinated approach to care, using various health care professionals and featuring an appropriate frequency of office visits, short waiting times, supportive patient counseling, and controlled formularies. The outcomes of the management of hypertension will need to be monitored, in keeping with the requirements of organizations that monitor quality, such as the Health Plan Employer Data and Information Set (HEDIS). These outcomes may be divided into three categories: immediate (e.g., blood pressure levels, percentage of adherence to therapy), intermediate (e.g., cardiac or renal function, health resource utilization), and long-term (e.g., morbidity and mortality, cost-effectiveness).

Hypertension specialists may play an important role in providing more cost-effective management of high blood pressure by adapting national guidelines for local implementation, providing guidance for new drugs and diagnostic methods, and managing patients with identifiable causes of hypertension, resistance to therapy, or complex concomitant conditions.

Drug Interactions. As shown in table 11, some drug interactions may be helpful. For example, diuretics that act on different sites in the nephron, such as furosemide and thiazides, increase natiuresis and diuresis, and certain calcium antagonists reduce the required amount of cyclosporine. Other interactions are deleterious: nonsteroidal anti-inflammatory drugs (NSAIDs) may blunt the action of diuretics, beta-blockers, and ACE inhibitors.

Dosage and Followup

Therapy for most patients (uncomplicated hypertension, stages 1 and 2) should begin with the lowest dosage listed in table 7 to prevent

adverse effects of too great or too abrupt a reduction in blood pressure. If blood pressure remains uncontrolled after 1 to 2 months, the next dosage level should be prescribed. It may take months to control hypertension adequately while avoiding adverse effects of therapy. Most antihypertensive medications can be given once daily, and this should be the goal to improve patient adherence. Home or office blood pressure measurement in the early morning before patients have taken their daily dose is useful to ensure adequate modulation of the surge in blood pressure after arising. Measurements in the late afternoon or evening help monitor control across the day. Treatment goals based on out-of-office measurements should be lower than those based on office recordings[45Pr] (see chapter 2).

Initial Drug Therapy

When the decision has been made to begin antihypertensive therapy (table 5) and if there are no indications for another type of drug, a diuretic or beta-blocker should be chosen because numerous randomized controlled trials have shown a reduction in morbidity and mortality with these agents (figures 6 and 7).

As shown in table 9 and figure 8, there are compelling indications for specific agents in certain clinical conditions, based on outcomes data from RCTs. In other situations where outcomes data are not yet available, there are indications for other agents and the choice should be individualized, using the agent that most closely fits the patient's needs.[134Pr]

If the response to the initial drug choice is inadequate after reaching the full dose, two options for subsequent therapy should be considered (see figure 8 for treatment algorithm):

- If the patient is tolerating the first choice well, add a second drug from another class.
- If the patient is having significant adverse effects or no response, substitute an agent from another class.

If a diuretic is not chosen as the first drug, it is usually indicated as a second-step agent because its addition will enhance the effects of other agents. If addition of a second agent controls blood pressure satisfactorily, an attempt to withdraw the first agent may be considered.[135F]

Before proceeding to each successive treatment step, clinicians should consider possible reasons for lack of responsiveness to therapy, including those listed in table 12.

High-Risk Patients

Although similar general approaches are advocated for all patients with hypertension, modifications may be needed for those with stage 3 hypertension, those in risk group C, or those at especially high risk for a coronary event or stroke (table 5). Drug therapy should begin with minimal delay. Although some patients may respond adequately to a single drug, it is often necessary to add a second or third agent after a short interval if control is not achieved. The intervals between changes in the regimen should be decreased, and the maximum dose of some drugs may be increased. In some patients, it may be necessary to start treatment with more than one agent. Patients with average SBP of 200 mm Hg or greater and average DBP of 120 mm Hg or greater require more immediate therapy and, if symptomatic target organ damage is present, may require hospitalization.

Step-Down Therapy

An effort to decrease the dosage and number of antihypertensive drugs should be considered after hypertension has been controlled effectively for at least 1 year. The reduction should be made in a deliberate, slow, and progressive manner. Step-down therapy is more often successful in patients who also are making lifestyle modifications.[80Ra] Patients whose drugs have been discontinued should have scheduled followup visits because blood pressure usually rises again to hypertensive levels, sometimes months or years after discontinuance, especially in the absence of sustained improvements in lifestyle.

Table 12

Causes of Inadequate Responsiveness to Therapy

Pseudoresistance
- "White-coat hypertension" or office elevations
- Pseudohypertension in older patients
- Use of regular cuff on very obese arm

Nonadherence to therapy
- (See table 13)

Volume overload
- Excess salt intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

Drug-related causes
- Doses too low
- Wrong type of diuretic
- Inappropriate combinations
- Rapid inactivation (e.g., hydralazine)
- Drug actions and interactions
  - Sympathomimetics
  - Nasal decongestants
  - Appetite suppressants
  - Cocaine and other illicit drugs
  - Caffeine
  - Oral contraceptives
  - Adrenal steroids
  - Licorice (as may be found in chewing tobacco)
  - Cyclosporine, tacrolimus
  - Erythropoietin
  - Antidepressants
  - Nonsteroidal anti-inflammatory drugs

Associated conditions
- Smoking
- Increasing obesity
- Sleep apnea
- Insulin resistance/hyperinsulinemia
- Ethanol intake of more than 1 oz (30 mL) per day
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (arteritis)
- Organic brain syndrome (e.g., memory deficit)

Identifiable causes of hypertension
- (See chapter 2)

J-Curve Hypothesis

Concerns have been raised that lowering DBP too much may increase the risk for coronary events by lowering diastolic perfusion pressure in the coronary circulation—the so-called J-curve hypothesis.[136Pr] The J-curve also has been detected in the placebo group of clinical trials of older persons with hypertension.[137F,138F] The J-curve concern may be more relevant to patients with both hypertension and preexisting coronary disease[136Pr] and to those with pulse pressure greater than 60 mm Hg.[139F] On the other hand, data support a progressive reduction in both cerebrovascular disease[74Re] and renal disease[75F] with even greater reductions in blood pressure. All available evidence supports the value of the reduction of DBP and SBP at all ages to the levels achieved in clinical trials—usually DBP to below 90 mm Hg and SBP to below 140 mm Hg in patients with isolated systolic hypertension.[140Ra,141Pr,142Ra] In trials of persons with isolated systolic hypertension, no increase in cardiovascular morbidity and mortality was observed, despite further reductions of DBP.

Considerations for Adherence to Therapy

Poor adherence to antihypertensive therapy remains a major therapeutic challenge[143Pr] contributing to the lack of adequate control in more than two-thirds of patients with hypertension (see chapter 1). As attempts to improve adherence are made, patients have the right and responsibility to be active and well-informed participants in their own care and to achieve maximal physical and emotional well-being. Health care professionals have the responsibility to provide patients with complete and accurate information about their health status, allowing patients the opportunity to participate in their care and to achieve goal blood pressure.

Followup Visits

Achieving and maintaining target blood pressure often requires continuing encouragement for lifestyle modification and medication adjustment. Most patients should be seen within 1 to 2 months after the initiation of therapy to determine the adequacy of hypertension control, the degree of patient adherence, and the presence of adverse effects. Associated medical problems—including target organ damage, other major risk factors, and laboratory test abnormalities—also play a part in determining the frequency of patient followup. Visits to other members of the health care team may provide opportunities for more frequent followup.[37Pr] Once blood pressure is stabilized, followup at 3- to 6-month intervals (depending on patient status) is generally appropriate. In some patients, particularly older persons and those with orthostatic symptoms, monitoring should include blood pressure measurement in the seated position and, to recognize postural hypotension, after standing quietly for 2 to 5 minutes.

Strategies for Improving Adherence to Therapy and Control of High Blood Pressure

Various strategies may improve adherence significantly (table 13). The choice and application of specific strategies depend on individual patient characteristics, and health care providers are not expected to apply all of them at any one time or to all patients. In particular, pharmacists should be encouraged to monitor patients' use of medications, to provide information about potential adverse effects, and to avoid drug interactions. Nurse-managed clinics offer attractive opportunities to improve adherence and outcomes.[37Pr,144Pr] The services of other members of the health care team, such as those who provide counseling in nutrition or exercise, should be used.

Resistant Hypertension

Hypertension should be considered resistant if blood pressure cannot be reduced to below 140/90 mm Hg in patients who are adhering to an adequate and appropriate triple-drug regimen that includes a diuretic, with all three drugs prescribed in near maximal doses. For older patients with isolated systolic hypertension, resistance is

Table 13

General Guidelines to Improve Patient Adherence to Antihypertensive Therapy

- Be aware of signs of patient nonadherence to antihypertensive therapy.
- Establish the goal of therapy: to reduce blood pressure to nonhypertensive levels with minimal or no adverse effects.
- Educate patients about the disease, and involve them and their families in its treatment. Have them measure blood pressure at home.
- Maintain contact with patients; consider telecommunication.
- Keep care inexpensive and simple.
- Encourage lifestyle modifications.
- Integrate pill-taking into routine activities of daily living.
- Prescribe medications according to pharmacologic principles, favoring long-acting formulations.
- Be willing to stop unsuccessful therapy and try a different approach.
- Anticipate adverse effects, and adjust therapy to prevent, minimize, or ameliorate side effects.
- Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy.
- Encourage a positive attitude about achieving therapeutic goals.
- Consider using nurse case management.

defined as failure of an adequate triple-drug regimen to reduce SBP to below 160 mm Hg.

Of the various causes of true resistance listed in table 12, one of the most common is volume overload due to inadequate diuretic therapy.[145Pr] Frequently, a cause for resistance can be recognized and overcome. However, if goal blood pressure cannot be achieved without intolerable adverse effects, even suboptimal reduction of blood pressure contributes to decreased morbidity and mortality. Patients who have resistant hypertension or who are unable to tolerate antihypertensive therapy may benefit from referral to a hypertension specialist.

Hypertensive Crises: Emergencies and Urgencies

Hypertensive emergencies are those rare situations that require immediate blood pressure reduction (not necessarily to normal ranges) to prevent or limit target organ damage. Examples include hypertensive encephalopathy, intracranial hemorrhage, unstable angina pectoris, acute myocardial infarction, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, or eclampsia. Hypertensive urgencies are those situations in which it is desirable to reduce blood pressure within a few hours. Examples include upper levels of stage 3 hypertension, hypertension with optic disk edema,

progressive target organ complications, and severe perioperative hypertension. Elevated blood pressure alone, in the absence of symptoms or new or progressive target organ damage, rarely requires emergency therapy.

Parenteral drugs for hypertensive emergencies are listed in table 10. Most hypertensive emergencies are treated initially with parenteral administration of an appropriate agent. Hypertensive urgencies can be managed with oral doses of drugs with relatively fast onset of action. The choices include loop diuretics, beta-blockers, ACE inhibitors, alpha$_2$-agonists, or calcium antagonists.

The initial goal of therapy in hypertensive emergencies is to reduce mean arterial blood pressure by no more than 25 percent (within minutes to 2 hours), then toward 160/100 mm Hg within 2 to 6 hours, avoiding excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia. Although sublingual administration of fast-acting nifedipine has been widely used for this purpose, several serious adverse effects have been reported with its use[124Pr] and the inability to control the rate or degree of fall in blood pressure makes this agent unacceptable. The routine use of sublingual nifedipine whenever blood pressure rises beyond a predetermined level in postoperative or nursing home patients is also not appropriate. Rather, the proximate causes of the elevated blood pressure, such as pain or a distended urinary bladder, should be addressed. Blood pressure should be monitored over 15- to 30-minute intervals; if it remains greater than 180/120 mm Hg, one of the previously mentioned oral agents may be given. If such high levels of blood pressure are frequent, adequate doses of long-acting agents should be provided.

SUMMARY

- Modifying lifestyles in populations can have a major protective effect against high blood pressure and cardiovascular disease.
- Lowering blood pressure decreases deaths from stroke, coronary events, and heart failure; slows progression of renal failure; prevents progression to more severe hypertension; and reduces all-cause mortality.
- A diuretic and/or a beta-blocker should be chosen as initial therapy unless there are compelling or specific indications for another drug.
- Management strategies can improve adherence through the use of multidisciplinary teams.
- The reductions in cardiovascular events demonstrated in randomized controlled trials have important implications for managed care organizations.
- Strategies for managing hypertensive emergencies and urgencies are described.

CHAPTER 4

SPECIAL POPULATIONS AND SITUATIONS

HYPERTENSION IN RACIAL AND ETHNIC MINORITIES

The United States is a diverse nation composed of individuals from many cultures. The 1990 census reported that the U.S. population was 0.8 percent American Indians, Aleuts, and Inuits; 2.9 percent Asians and Pacific Islanders; 9.0 percent persons of Hispanic origin; 12.1 percent African Americans; and 80.3 percent white.[146] (These self-reported categories are not mutually exclusive; thus, the total is greater than 100 percent.) In the past decade, the country has experienced a marked increase in minority populations and the number of immigrants. This trend is expected to continue.

As immigrant populations acculturate, their risk for cardiovascular disease changes.[147F] The prevalence of hypertension differs among racial and ethnic groups compared with the general population.[148Pr] For example, American Indians have the same prevalence as, or a higher prevalence than, the general population; among Hispanics, blood pressure is generally the same as or lower than that of non-Hispanic whites, despite a high prevalence of obesity and type 2 diabetes mellitus. It also appears that South Asians are more responsive to various antihypertensive medications than whites.[149C,150X] Evidence shows that hypertension awareness, treatment, and control in some groups, especially those with generally lower socioeconomic status, require more focused hypertension education and intervention programs.[148Pr,151X,152X,153X]

The prevalence of hypertension in African Americans is among the highest in the world. Compared with whites, hypertension develops earlier in life and average blood pressures are much higher in African Americans. African Americans have higher rates of stage 3 hypertension than whites, causing a greater burden of hypertension complications.[14Pr,24X] This earlier onset, higher prevalence, and greater rate of stage 3 hypertension in African Americans is accompanied by an 80-percent higher stroke mortality rate, a 50-percent higher heart disease mortality rate, and a 320-percent greater rate of hypertension-related end-stage renal disease than seen in the general population.[154X,155F]

Available evidence indicates that, compared with whites, African Americans receiving adequate treatment will achieve similar overall declines in blood pressure and may experience a lower incidence of cardiovascular disease.[156Ra,157F] However, African Americans often do not receive treatment until blood pressure has been elevated a long time and target organ damage is present. This also may account for the higher incidence of hypertension-related morbidity and mortality in the African American population, including end-stage renal disease.[155F]

Because of the high prevalence of cardiovascular risk factors in African Americans—such as obesity, cigarette smoking, and type 2 diabetes—as well as increased responsiveness to reduced salt intake, lifestyle modifications are particularly important.

In African Americans, as well as in whites, diuretics have been proven in controlled trials to reduce hypertensive morbidity and mortality; thus, diuretics should be the agent of first choice in the absence of conditions that prohibit their use. Calcium antagonists and alpha-beta-blockers are also effective in lowering blood pressure.[129Ra,158Ra] Monotherapy with beta-blockers or ACE inhibitors is less effective, but the addition of diuretics markedly improves response. However, these agents are indicated regardless of ethnicity when patients have other specific indications (e.g., beta-blockers for angina or post-myocardial infarction, ACE inhibitors for diabetic nephropathy or left ventricular systolic dysfunction).[159Ra]

Because of their greater prevalence of stage 3 hypertension, many African American patients require multidrug therapy. Every effort should be made to achieve a goal blood pressure of below 140/90 mm Hg. In patients with renal insufficiency, recent data suggest that reducing blood pressure to an even lower level may be beneficial (see discussion of renal disease in this chapter).

Hypertension in Children and Adolescents

The fifth Korotkoff sound is now used to define DBP for all ages. Definitions of hypertension take into account age and height by sex. Blood pressure at the 95th percentile or greater is considered elevated (table 14). Clinicians should be alert to the possibility of identifiable causes of hypertension in younger children. Lifestyle interventions should be recommended, with pharmacologic therapy instituted for higher levels of blood pressure or if there is insufficient response to lifestyle modifications. Although the recommendations for choice of drugs are similar in children and adults, dosages of antihypertensive medication should be smaller and adjusted very carefully for children. ACE inhibitors and angiotensin II receptor blockers should not be used in pregnant or sexually active girls.

Uncomplicated elevated blood pressure alone should not be a reason to restrict asymptomatic children from participating in physical activities, particularly because exercise may lower blood pressure and prevent hypertension. Use of anabolic steroid hormones for the purpose of bodybuilding should be strongly discouraged. Efforts should be made to discover other risk factors (e.g., smoking) in children, and interventions should be made if they are present. Detailed recommendations regarding hypertension in children and adolescents can be found in the 1996 report by the NHBPEP Working Group on Hypertension Control in Children and Adolescents.[160Pr]

Hypertension in Women

Large, long-term clinical trials of antihypertensive treatment have included both men and women and have not demonstrated clinically significant sex differences in blood pressure response and outcomes.[128M] Recent trials of older persons support a similar approach to hypertension management in men and women.[26Pr]

Hypertension Associated With Oral Contraceptives

Women taking oral contraceptives experience a small but detectable increase in both SBP and DBP, usually within the normal range. Hypertension has been reported to be two to three times more common in women taking oral contraceptives, especially in obese and older women, than in those not taking oral contraceptives.[161Pr] Women age 35 and older who smoke cigarettes should be strongly counseled to quit; if they continue to smoke, they should be discouraged from using oral contraceptives.

If hypertension develops in women taking oral contraceptives, it is advisable to stop their use. Blood pressure will normalize in most cases within a few months. If high blood pressure persists, if the risks for pregnancy are considered to be greater than the risks for hypertension, and if other contraceptive methods are not suitable,

Table 14

95TH PERCENTILE OF BLOOD PRESSURE BY SELECTED AGES IN GIRLS AND BOYS, BY THE 50TH AND 75TH HEIGHT PERCENTILES*

Age (Years)	Girls' SBP/DBP		Boys' SBP/DBP	
	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

* Adapted from the report by the NHBPEP Working Group on Hypertension Control in Children and Adolescents.[160] SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

then oral contraceptives may have to be continued and therapy for hypertension begun. A prudent approach to the use of oral contraceptives is to prescribe no more than a 6-month supply at a time in order to measure blood pressure on a semiannual basis.

Hypertension in Pregnancy

Chronic hypertension is high blood pressure that is present and observable before pregnancy or that is diagnosed before the 20th week of gestation. The goal of treatment for women with chronic hypertension in pregnancy is to minimize the short-term risks of elevated blood pressure to the mother while avoiding therapy that compromises the well-being of the fetus. If taken before pregnancy, diuretics and most other antihypertensive drugs, except ACE inhibitors and angiotensin II receptor blockers, may be continued. Methyldopa has been evaluated most extensively and is therefore recommended for women whose hypertension is first diagnosed during pregnancy. Beta-blockers compare favorably with methyldopa with respect to efficacy and are considered safe in the latter part of pregnancy; however, their use in early pregnancy may be associated with growth retardation of the fetus (table 15). ACE inhibitors and angiotensin II receptor blockers should be avoided because serious neonatal problems, including renal failure and death, have been reported when mothers have taken these agents during the last two trimesters of pregnancy.[162Pr]

Preeclampsia. Preeclampsia, a pregnancy-specific condition, is increased blood pressure accompanied by proteinuria, edema, or both and at times by abnormalities of coagulation and renal and liver function that may progress rapidly to a convulsive phase, eclampsia. Preeclampsia occurs primarily during first pregnancies and after the 20th week of gestation. It may be superimposed on preexisting chronic hypertension. Large trials have not confirmed the benefit of prophylactic low-dose aspirin or supplemental calcium to prevent preeclampsia.[163Pr,164Pr] A detailed summary of hypertension in pregnancy was published in a report by the NHBPEP Working Group on High Blood Pressure in Pregnancy.[165Pr] More recent reviews have been published.[162Pr,163Pr]

Table 15

Antihypertensive Drugs Used in Pregnancy*

The report of the NHBPEP Working Group on High Blood Pressure in Pregnancy[165] permits continuation of drug therapy in women with chronic hypertension (except for ACE inhibitors). In addition, angiotensin II receptor blockers should not be used during pregnancy. In women with chronic hypertension with diastolic levels of 100 mm Hg or greater (lower when end organ damage or underlying renal disease is present) and in women with acute hypertension when levels are 105 mm Hg or greater, the following agents are suggested.

Suggested Drug	Comments
Central alpha-agonists	Methyldopa (C) is the drug of choice recommended by the NHBPEP Working Group.[165]
Beta-blockers	Atenolol (C) and metoprolol (C) appear to be safe and effective in late pregnancy. Labetalol (C) also appears to be effective (alpha- and beta-blockers).
Calcium antagonists	Potential synergism with magnesium sulfate may lead to precipitous hypotension. (C)
ACE inhibitors, angiotensin II receptor blockers	Fetal abnormalities, including death, can be caused, and these drugs should not be used in pregnancy. (D)
Diuretics	Diuretics (C) are recommended for chronic hypertension if prescribed before gestation or if patients appear to be salt-sensitive. They are not recommended in preeclampsia.
Direct vasodilators	Hydralazine (C) is the parenteral drug of choice based on its long history of safety and efficacy. (C)

* Adapted from Sibai[162] and Lindheimer.[163] There are several other antihypertensive drugs for which there are very limited data. The U.S. Food and Drug Administration classifies pregnancy risk as follows: C, adverse effects in animals; no controlled trials in humans; use if risk appears justified; D, positive evidence of fetal risk. ACE indicates angiotensin-converting enzyme.

Hormone Replacement Therapy and Blood Pressure Response

The presence of hypertension is not a contraindication to postmenopausal estrogen replacement therapy. A recent study indicated that blood pressure does not increase significantly with hormone replacement therapy in most women with and without hypertension and that hormone replacement therapy has a beneficial effect on overall cardiovascular risk factor profiles.[166Ra] However, a few women may experience a rise in blood pressure attributable to estrogen therapy. Therefore, it is recommended that all women treated with hormone replacement therapy have their blood pressure monitored more frequently after such therapy is instituted. The effect of transdermal estrogen and progestogen on blood pressure has not been established.

Hypertension in Older Persons

Hypertension is extremely common in older Americans. Among Americans age 60 and older examined in the NHANES III, elevated blood pressure was found in 60 percent of non-Hispanic whites, 71 percent of non-Hispanic African Americans, and 61 percent of Mexican Americans.[24X] Especially among older persons, SBP is a better predictor of events (coronary heart disease, cardiovascular disease, heart failure, stroke, end-stage renal disease, and all-cause mortality) than is DBP.[26Pr] Recently, it has become clear that an elevated pulse pressure (SBP minus DBP), which indicates reduced vascular compliance in large arteries, may be an even better marker of increased cardiovascular risk than either SBP or DBP alone.[139F] This is particularly relevant to older individuals who frequently have an isolated elevation of SBP (140 mm Hg or greater with a DBP below 90 mm Hg) (table 2). Those with stage 1 isolated systolic hypertension are at significantly increased cardiovascular risk, but the benefits of treatment in those individuals have not yet been demonstrated in a controlled trial.[167F]

Primary hypertension is by far the most common form of hypertension in older persons. However, clinicians must recognize that certain identifiable causes of hypertension (e.g., atherosclerotic renovascular hypertension, primary aldosteronism) may occur more frequently in older persons, especially in those whose hypertension first presented after age 60 or is resistant to treatment.[145Pr]

Blood pressure must be measured in older persons with special care because some older persons have pseudohypertension (falsely high sphygmomanometer readings) due to excessive vascular stiffness.[168] In addition, more older persons with hypertension, especially women, may have "white-coat hypertension" and excessive variability in SBP.[169X] In the absence of target organ damage, clinicians should consider pseudohypertension or "white-coat hypertension" and should obtain readings outside the office (see chapter 2). In addition, older patients are more likely than younger patients to exhibit an orthostatic fall in blood pressure and hypotension; thus, in older patients, blood pressure should always be measured in the standing as well as seated or supine positions.[170X]

Treatment of hypertension in older persons has demonstrated major benefits (figure 7). Large trials of patients older than age 60 have shown that antihypertensive drug therapy reduces stroke, CHD, cardiovascular disease, heart failure, and mortality.[140Ra,171Ra,172Ra,173Ra,174Ra]

Hypertension therapy in older persons, as in younger persons, should begin with lifestyle modifications.[26Pr] Older patients will respond to modest salt reduction and weight loss.[80Ra] If goal blood pressure is not achieved, then pharmacologic treatment is indicated. The starting dose in older patients should be about half of that used in younger patients. Thiazide diuretics or beta-blockers in combination with thiazide diuretics are recommended because they are effective in reducing mortality and morbidity in older persons with hypertension as shown in multiple randomized controlled trials.[120M,171Ra] When compared to each other, diuretics (hydrochlorothiazide with amiloride hydrochloride) are superior to the beta-blocker atenolol.[172Ra] In older patients with isolated systolic hypertension, diuretics are preferred because they have significantly reduced multiple endpoint events.[171Ra] In addition, an RCT in such patients taking the dihydropyridine nitrendipine showed a 42-percent reduction in fatal and nonfatal stroke over an average 2-year interval.[140Ra] The concomitant reductions in coronary events and heart failure did not reach statistical significance although a favorable trend was reported and all cardiovascular disease mortality was significantly reduced. Because nitrendipine is not available in the United States, other long-acting dihydropyridine calcium antagonists are considered to be appropriate alternatives in these patients.

The goal of treatment in older patients should be the same as in younger patients (to below 140/90 mm Hg if at all possible), although an interim goal of SBP below 160 mm Hg may be necessary in those patients with marked systolic hypertension.[26Pr] Any reduction in blood pressure appears to confer benefit—the closer to normal, the greater the benefit. Drugs that exaggerate postural changes in blood pressure (peripheral adrenergic blockers, alpha-blockers, and high-dose diuretics) or drugs that can cause cognitive dysfunction (central $alpha_2$-agonists) should be used with caution. Additional recommendations about hypertension in older persons can be found in the report by the NHBPEP Working Group on Hypertension in the Elderly.[26Pr]

Patients With Hypertension and Coexisting Cardiovascular Diseases

Patients With Cerebrovascular Disease

Clinically evident cerebrovascular disease is an indication for antihypertensive treatment. However, immediately after the occurrence of an ischemic cerebral infarction, it is appropriate to withhold treatment (unless blood pressure is very high) until the situation has been stabilized. Even when treatment has been withheld temporarily, the eventual goal is to reduce blood pressure gradually while avoiding orthostatic hypotension. Patients with acute ischemic stroke who are treated with fibrinolytic agents require careful blood pressure monitoring, especially over the first 24 hours after starting treatment. SBP of 180 mm Hg or greater or DBP of 105 mm Hg or greater may be controlled with intravenous agents with careful monitoring for worsening of neurological status.[175C]

Patients With Coronary Artery Disease

Patients with coronary artery disease and hypertension are at particularly high risk for cardiovascular morbidity and mortality. The benefits and safety of antihypertensive therapy in such patients are well established.[176Pr,177Pr] Excessively rapid lowering of blood pressure, particularly when it causes reflex tachycardia and sympathetic activation, should be avoided. Blood pressure should be lowered to the usual target range (below 140/90 mm Hg), and even lower blood pressure is desirable if angina persists.

Beta-blockers or calcium antagonists may be specifically useful in patients with hypertension and angina pectoris; however, short-acting calcium antagonists should not be used.[125M,178Re179Re] After myocardial infarction, beta-blockers without intrinsic sympathomimetic activity should be given because they reduce the risk for subsequent myocardial infarction or sudden cardiac death. ACE inhibitors are also useful after myocardial infarction, especially with left ventricular systolic dysfunction, to prevent subsequent heart failure and mortality.[176Pr]

If beta-blockers are ineffective or contraindicated, verapamil hydrochloride or diltiazem hydrochloride may be used because they have been shown to reduce cardiac events and mortality modestly in two circumstances: (1) following non-Q-wave myocardial infarction, and (2) after myocardial infarction with preserved left ventricular function (LVH).[119Pr,180Pr,181Pr]

Some patients with hypertension, especially when accompanied by severe LVH, may experience angina without evidence of coronary atherosclerosis. This is thought to reflect an imbalance between myocardial oxygen supply and demand, due in part to changes in the coronary microcirculation. Treatment should be directed at blood pressure control, reversal of LVH, and avoidance of tachycardia, which may exacerbate the supply-demand mismatch.

Patients With Left Ventricular Hypertrophy

Development of LVH permits cardiac adaptation to the increased afterload imposed by elevated arterial pressure. However, LVH is a major independent risk factor for sudden cardiac death, myocardial infarction, stroke, and other cardiovascular morbid and mortal events.[182F,183F] Evidence shows that antihypertensive agents (except direct vasodilators such as hydralazine

and minoxidil), weight reduction, and decrease of excessive salt intake are capable of reducing increased left ventricular mass and wall thickness.[184Pr] In one study in men with hypertension, treatment with a diuretic and an ACE inhibitor was better than treatment with other drug classes tested for regressing LVH at 1 year.[185Ra] Observational data indicate that the regression of electrocardiographic evidence of LVH is associated with a reduction in the risk for cardiovascular events.[186F] However, no controlled studies demonstrate that such reversal of LVH offers additional benefits beyond that offered by reduction of blood pressure.[187Pr] The electrocardiogram remains valuable not only for detecting left atrial hypertrophy and LVH but also for identifying evidence of myocardial ischemia and arrhythmia.[188Pr] Echocardiography is more sensitive and specific for identifying LVH, but it is too expensive for routine use. Limited echocardiography will identify LVH at a cost that may justify its use in some patients (e.g., those with untreated stage 1 hypertension, no cardiovascular risk factors, no evidence of clinical cardiovascular disease, and no target organ damage).[189Pr]

Patients With Cardiac Failure

In patients with hypertension, structural alterations in the left ventricle (LVH or left ventricular remodeling with dilation) as well as myocardial ischemia from coronary artery atherosclerosis may contribute to the development of heart failure. Some patients with hypertension (current or past) develop heart failure with a normal ejection fraction, implying diastolic dysfunction. Reports from the Framingham Heart Study have demonstrated that hypertension continues to be the major cause of left ventricular failure in the United States.[190Pr] Control of elevated arterial pressure using lifestyle changes and drug therapy improves myocardial function and prevents and reduces heart failure and cardiovascular mortality.[119Pr] After myocardial infarction, therapy with ACE inhibitors prevents subsequent heart failure and reduces morbidity and mortality.[191Ra] In treating heart failure, ACE inhibitors, when used alone or in conjunction with digoxin or diuretics, are effective in reducing morbidity and mortality.[192M] When ACE inhibitors are contraindicated or not tolerated, the vasodilator combination of hydralazine hydrochloride and isosorbide dinitrate is also effective in these patients.[193Ra] The alpha-beta-blocker carvedilol added to ACE inhibitors has been shown to be beneficial,[194Ra,195Ra] and, in one trial, the angiotensin II receptor blocker losartan potassium was superior to captopril in reducing mortality.[196Ra] The dihydropyridine calcium antagonists amlodipine besylate and felodipine have been demonstrated to be safe in treating angina and hypertension in patients with advanced left ventricular dysfunction when used in addition to ACE inhibitors, diuretics, or digoxin;[197Ra,198Ra] other calcium antagonists are not recommended in these patients.

Patients With Peripheral Arterial Disease

Hypertension is one of the major risk factors for the development of carotid atherosclerosis and peripheral arterial disease with intermittent claudication and aneurysms. However, data are not available to determine whether antihypertensive therapy will alter the course of these processes. Early multicenter trials demonstrated a reduction in deaths from dissecting aortic aneurysms.[199Ra]

Patients With Hypertension and Other Coexisting Diseases

Patients With Renal Parenchymal Disease

Pathophysiology. Hypertension may result from any form of renal disease that reduces the number of functioning nephrons, leading to sodium and water retention.[200Pr] Hypertensive nephrosclerosis is among the most common causes of progressive renal disease, particularly in African Americans.[201X] Followup of large numbers of men screened for the Multiple Risk Factor Intervention Trial and of male veterans has provided the most conclusive and direct evidence of a relationship between blood pressure and end-stage renal disease.[202F,203F]

Strategies for Slowing Progressive Renal Failure in Patients With Hypertension. Early detection of hypertensive renal damage is essential. Small elevations of serum creatinine reflect significant losses in glomerular filtration rate. Evaluation should include urinalysis to detect proteinuria or hematuria and possibly renal sonography to exclude lower tract obstruction, to exclude autosomal dominant polycystic kidney disease, and to determine the size of the kidneys.[204Pr] Reversible causes of renal failure always should be sought and treated.

Blood pressure should be controlled to 130/85 mm Hg—or lower (125/75 mm Hg) in patients with proteinuria in excess of 1 gram per 24 hours—with whatever antihypertensive therapy is necessary.[75F,155F] Reducing dietary sodium to a level lower than that recommended for uncomplicated hypertension (less than 100 mmol per day of sodium) helps control high blood pressure in patients with renal insufficiency.[204Pr] If dietary protein restriction is instituted, close attention must be paid to total energy (caloric) intake to prevent malnutrition. Restriction of dietary potassium and phosphorus in patients with creatinine clearances below 30 mL per minute is needed to prevent hyperkalemia and to help prevent secondary hyperparathyroidism.

Antihypertensive Drug Recommendations for Patients With Hypertension and Renal Disease. The most important action to slow progressive renal failure is to lower blood pressure to goal. All classes of antihypertensive drugs are effective, and, in most cases, multiple antihypertensive drugs may be needed.[204Pr,205Pr] Impressive results have been achieved with ACE inhibitors in patients with type 1 diabetic nephropathy,[206Ra] in patients with proteinuria greater than 1 gram per 24 hours,[207Ra] and in patients with renal insufficiency.[208Ra,209M] Consequently, patients with hypertension who have renal insufficiency should receive, unless contraindicated, an ACE inhibitor (in most cases, along with a diuretic) to control hypertension and to slow progressive renal failure.[206Ra,208Ra,209M] In patients with a creatinine level of 265.2 µmol/L (3 mg/dL) or greater, ACE inhibitors should be used with caution.

An initial transient decrease in glomerular filtration rate may occur during the first 3 months of treatment as blood pressure is lowered.[207Ra] If patients are euvolemic and creatinine rises 88.4 µmol/L (1 mg/dL) above baseline levels, creatinine and potassium should be remeasured after several days; if they remain persistently elevated, consideration should be given to the diagnosis of renal artery stenosis and ACE inhibitors or angiotensin II receptor blockers discontinued because these drugs can markedly reduce renal perfusion in patients with bilateral renal artery stenosis or renal artery stenosis to a solitary kidney.[210Pr]

Thiazide diuretics are not effective with advanced renal insufficiency (serum creatinine level of 221.0 µmol/L [2.5 mg/dL] or greater), and loop diuretics are needed (often at relatively large doses). Combining a loop diuretic with a long-acting thiazide diuretic, such as metolazone, is effective in patients resistant to a loop diuretic alone. Potassium-sparing diuretics should be avoided in patients with renal insufficiency.

Patients With Renovascular Disease

Hemodynamically significant renal artery stenosis may be associated with all stages of hypertension, but it is more commonly found with stage 3 or resistant hypertension and, when bilateral, can lead to reduced kidney function (ischemic nephropathy).[211F]

Clinical clues to renovascular disease include (1) onset of hypertension before age 30, especially without a family history, or recent onset of significant hypertension after age 55; (2) an abdominal bruit, particularly if it continues into diastole and is lateralized; (3) accelerated or resistant hypertension; (4) recurrent (flash) pulmonary edema; (5) renal failure of uncertain cause, especially with a normal urinary sediment;

(6) coexisting, diffuse atherosclerotic vascular disease, especially in heavy smokers; and (7) acute renal failure precipitated by antihypertensive therapy, particularly ACE inhibitors or angiotensin II receptor blockers.

In patients with indications of renovascular disease, captopril-enhanced radionuclide renal scan, duplex Doppler flow studies, and magnetic resonance angiography may be used as noninvasive screening tests. Three-dimensional images can be obtained by spiral computed tomography, a technique that unfortunately requires intravenous contrast.[204Pr] Definitive diagnosis of renovascular disease requires renal angiography, which carries some risk, particularly radio-contrast-induced acute renal failure or atheroembolism in older patients.[212Pr]

Management. In younger patients with fibromuscular dysplasia, results of percutaneous transluminal renal angioplasty (PTRA) have been excellent and comparable to surgical revascularization.[213Re] Patients with normal renal function and atherosclerotic renal artery stenosis that is focal, unilateral, and nonostial, without widespread vascular disease, are managed similarly to those with fibromuscular dysplasia.[214Pr] Renal artery stenting has become an important adjunct to PTRA, being used to counteract elastic recoil and to abolish the residual stenosis often observed after PTRA.[215C]

Even though many patients with high-grade renal artery stenosis remain stable for prolonged periods, if blood pressure is well controlled,[216F] surgical revascularization or PTRA with renal artery stenting may be needed to preserve renal function.[204Pr]

Patients With Diabetes Mellitus

To detect evidence of autonomic dysfunction and orthostatic hypotension, blood pressure should be measured in the supine, sitting, and standing positions in all patients with diabetes mellitus; automated ambulatory blood pressure monitoring may be especially helpful (see chapter 2).

Antihypertensive drug therapy should be initiated along with lifestyle modifications, especially weight loss, to reduce arterial blood pressure to below 130/85 mm Hg. ACE inhibitors, alpha-blockers, calcium antagonists, and diuretics in low doses are preferred because of fewer adverse effects on glucose homeostasis, lipid profiles, and renal function.[217Pr,218Pr] Although beta-blockers may have adverse effects on peripheral blood flow, prolong hypoglycemia, and mask hypoglycemic symptoms, patients with diabetes who are treated with diuretics and beta-blockers experience a similar or greater reduction of CHD and total cardiovascular events compared with persons without diabetes.[219Ra,220Re] In patients with diabetic nephropathy, ACE inhibitors are preferred.[206Ra,221Ra,222M] If ACE inhibitors are contraindicated or are not well tolerated, angiotensin II receptor blockers may be considered. Renoprotection also has been shown by the use of a calcium antagonist.[223Ra,224Ra]

Insulin Resistance. Obese patients with hypertension have resistance to insulin-mediated glucose uptake by skeletal muscle, which can lead to impaired glucose tolerance and type 2 diabetes.[218Pr] Some nonobese persons with hypertension and persons with normal blood pressure who have first-degree relatives with hypertension also have insulin resistance. It is uncertain whether the higher peripheral insulin levels or the insulin resistance may cause hypertension.[225Pr] These metabolic disturbances as well as the hypertension respond to weight loss, exercise, insulin-sensitizing agents, vasodilating antihypertensive drugs, and certain lipid-lowering drugs.[226Pr]

Patients With Dyslipidemia

The common coexistence and increased risk of dyslipidemia and hypertension mandate aggressive management of both conditions.[227Pr] Because lifestyle modifications are the first approach to the treatment of both conditions, great emphasis must be placed on control of overweight; reduced intake of saturated fat, cho-

lesterol, sodium chloride, and alcohol; and increased physical activity in patients with elevated lipids and high blood pressure.

In high doses, thiazide diuretics and loop diuretics can induce at least short-term increases in levels of total plasma cholesterol, triglycerides, and LDL cholesterol.[228Pr] Dietary modifications can reduce or eliminate these effects.[77Ra,229F] Low-dose thiazide diuretics do not produce these effects.[230Ra] In the Systolic Hypertension in the Elderly Program and the Hypertension Detection and Follow-up Program, which both used diuretics as initial monotherapy or in combination, the risks for cerebrovascular and coronary events were reduced equally in persons with normal lipid levels and those with elevated lipid levels.[231F,232F]

Beta-blockers may increase levels of plasma triglycerides transiently and reduce levels of HDL cholesterol.[233F] Despite this, beta-blockers have been shown to reduce the rate of sudden death, overall mortality, and recurrent myocardial infarction in patients with previous myocardial infarction.[234M]

Alpha-blockers may decrease serum cholesterol concentration to a modest degree and increase HDL cholesterol.[230F] ACE inhibitors, angiotensin II receptor blockers, calcium antagonists, and central adrenergic agonists have clinically neutral effects on levels of serum lipids and lipoproteins.[228Pr]

Recent trials have shown that aggressive lipid reduction, especially with beta-hydroxy-beta-methylglutaryl CoA (HMG-CoA) reductase inhibitors (statin drugs), provides both primary and secondary protection against CHD.[235Ra,236Ra,237Ra,238M] Lifestyle changes and hypolipidemic agents should be used to reach appropriate goals in patients with hypertension and hyperlipidemia. Guidance in the selection of appropriate cholesterol-lowering therapy is available in the guidelines of the National Cholesterol Education Program.[239Pr]

Patients With Sleep Apnea

Obstructive sleep apnea is characterized by loud snoring and disrupted breathing or gasping during sleep, is more common in patients with hypertension, and is associated with a number of adverse clinical consequences.[240Re] Undiagnosed sleep apnea may explain the difficulty in controlling high blood pressure in some patients; improved hypertension control has been reported in patients after treatment of their sleep apnea.[241F]

Patients With Bronchial Asthma or Chronic Airway Disease

Elevated blood pressure is relatively common in acute asthma and may be related to treatment with systemic corticosteroids or beta-agonists.

Beta-blockers and alpha-beta-blockers may exacerbate asthma; therefore, these agents should not be used in patients with asthma except in special circumstances. In addition, the topical ophthalmic application of beta-blockers such as timolol maleate may worsen asthma.

Bronchial reactivity to histamine and kinin remains unchanged with ACE inhibitors, which are safe in most patients with asthma. If a cough related to ACE inhibitor use occurs, angiotensin II receptor blockers are an alternative.

Many over-the-counter medications sold as decongestants and cold and asthma remedies may contain a sympathomimetic agent that can raise blood pressure. Nevertheless, these medications are generally safe when taken in limited doses in patients with hypertension who are receiving adequate antihypertensive therapy.[242F] Cromolyn sodium, ipratropium bromide, or corticosteroids by inhalation can be used safely for nasal congestion in persons with hypertension.

Patients With Gout

Hyperuricemia is a frequent finding in patients with untreated hypertension and may reflect a decrease in renal blood flow. In addition, all diuretics can increase serum uric acid levels but

rarely induce acute gout.[243F] In patients with gout, diuretics should be avoided if possible. Diuretic-induced hyperuricemia does not require treatment in the absence of gout or urate stones.

Patients Undergoing Surgery

Blood pressure of 180/110 mm Hg or greater is associated with a greater risk for perioperative ischemic events. When possible, surgery should be delayed to bring blood pressure down to lower levels.[244Pr] The perioperative risk for any patient, and especially patients with hypertension, is in part related to the adrenergic arousal before, during, and after surgery.[245] Those without prior antihypertensive therapy may be best treated with cardioselective beta-blocker therapy before and after surgery.[246Ra]

Adequate potassium supplementation should be provided to correct hypokalemia well in advance of surgery. Surgical candidates who are controlling their blood pressure adequately with medication should be maintained on their regimen until the time of surgery, and therapy should be reinstated as soon as possible after surgery. If oral intake must be interrupted, parenteral therapy with diuretics, adrenergic inhibitors, vasodilators, ACE inhibitors, or transdermal clonidine hydrochloride may be used to prevent the rebound hypertension that may follow sudden discontinuation of some adrenergic-inhibiting agents. Two studies have indicated a need for caution with calcium antagonists because of an increase in surgical bleeding.[247F,248C]

Miscellaneous Causes for Increased Blood Pressure

Cocaine

The majority of cocaine-dependent individuals are normotensive, and no evidence suggests that ongoing cocaine abuse causes chronic hypertension.[249] However, cocaine abuse must now be considered in all patients presenting to an emergency department with hypertension-related problems. Clues include the presence of chest pain, tachycardia, dilated pupils, combativeness, altered mental status, and seizures. Cocaine may induce severe ischemia from coronary and cerebral vasoconstriction as well as acute renal failure due to rhabdomyolysis.[250]

Nitroglycerin is indicated to reverse cocaine-related coronary vasoconstriction,[251X] but its antihypertensive efficacy may be inadequate and other parenteral agents may be needed (table 10). Nonselective beta-blockers such as propranolol should generally be avoided because of the risk of a paradoxical rise in blood pressure as well as coronary vasoconstriction due to the exaggerated effect of catecholamines on unblocked alpha-receptors.[252Ra]

Amphetamines

Acute amphetamine toxicity is similar to that of cocaine but longer in duration, lasting up to several hours. Cerebral and systemic vasculitis and renal failure may occur. Treatment for amphetamine toxicity is similar to that for cocaine toxicity.

Immunosuppressive Agents

Immunosuppressive regimens based on cyclosporine, tacrolimus, and steroids increase blood pressure in 50 to 80 percent of recipients of solid organ transplants. When cyclosporine is used alone in nontransplant applications, hypertension develops in 25 to 30 percent of patients. The rise in blood pressure reflects widespread vasoconstriction. Renal vasoconstriction leads to reduced glomerular filtration and enhanced sodium reabsorption. Therapy is based on vasodilation, often including dihydropyridine calcium antagonists. Diuretics are effective but may exaggerate prerenal azotemia and may precipitate gout.[253Pr]

Erythropoietin

Recombinant human erythropoietin increases blood pressure in 18 to 45 percent of patients when used in the treatment of end-stage renal disease. Hypertension is produced by a rise in systemic vascular resistance, partly related to direct vascular effects of recombinant human ery-

thropoietin, and is not closely related to hematocrit or viscosity. Management includes optimal volume control, antihypertensive agents, and, in some cases, reducing the erythropoietin dose or changing administration from the intravenous to subcutaneous route.

Other Agents

Hypertension may be induced by numerous other chemical agents and toxins, such as mineralocorticoids and derivatives, anabolic steroids, monoamine oxidase inhibitors, lead, cadmium, and bromocriptine.[254Pr]

SUMMARY

- Racial and ethnic minority populations are growing segments of our society. The prevalence of hypertension in these populations differs across groups, and control rates are not as good as in the general population. Clinicians should be aware of these management challenges, taking social and cultural factors into account.
- Guidelines are provided for management of children and women with hypertension.
- In older persons, diuretics are preferred and long-acting dihydropyridine calcium antagonists may be considered.
- Specific therapy for patients with left ventricular hypertrophy, coronary artery disease, and heart failure are outlined.
- Patients with renal insufficiency with greater than 1 gram per day of proteinuria should be treated to a therapy blood pressure goal of 125/75 mm Hg; those with less proteinuria should be treated to a blood pressure goal of 130/85 mm Hg. ACE inhibitors have additional renoprotective effects over other antihypertensive agents.
- Patients with diabetes should be treated to a therapy blood pressure goal of below 130/85 mm Hg.
- Hypertension may coexist with various other conditions and may be induced by various pressor agents.

REFERENCES

These symbols are placed after the reference number for those citations provided in chapters 3 and 4 in the text. Some references may have more than one code depending on the component of the study cited, e.g., a randomized controlled trial having a long-term followup.

- **M** meta-analyses—an analysis of a compendium of experimental studies;
- **Ra** randomized controlled trials—also known as experimental studies;
- **Re** retrospective analysis—also known as case control studies;
- **F** prospective followup—also known as cohort studies, including historical cohort studies and long-term followup;
- **X** cross-sectional population studies—also known as prevalence studies;
- **Pr** previous review or position statements; and
- **C** clinical interventions (nonrandomized).

1. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population: data from the health examination surveys, 1960 to 1991. *Hypertension* 1995;26:60-69.
2. Data calculated by National Heart, Lung, and Blood Institute staff, J. Cutler, principal investigator, January 1997.
3. Manton KG, Corder L, Stallard E. Chronic disability trends in elderly United States populations: 1982-1994. *Proc Natl Acad Sci USA* 1997;94:2593-2598.
4. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993;153:154-183. Pr
5. National Heart, Lung, and Blood Institute. *Fact Book Fiscal Year 1996.* Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; 1997.
6. U.S. Renal Data System. *USRDS 1997 Annual Report.* Bethesda, MD: U.S. Department of Health and Human Services, National Institute of Diabetes and Digestive and Kidney Disease; 1997. X
7. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-1562. F
8. National Center for Health Statistics. *Health, United States, 1996.* Hyattsville, MD: Public Health Service; 1997.
9. Luepker RV, McGovern PG, Sprafka JM, Shahar E, Doliszny KM, Blackburn H. Unfavorable trends in the detection and treatment of hypertension: the Minnesota Heart Survey [abstract]. *Circulation* 1995;91:938.
10. Meissner I, Whisnant JP, Sheps S, et al. Stroke prevention: assessment of risk in a community. The SPARC study, part I: blood pressure trends, treatment, and control [abstract]. *Ann Neurol* 1997;42:433.
11. Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373-380.
12. Glynn RJ, Brock DB, Harris T, et al. Use of antihypertensive drugs and trends in blood pressure in the elderly. *Arch Intern Med* 1995;155:1855-1860.
13. U.S. Department of Health and Human Services. *Healthy People 2000: National Health Promotion and Disease Prevention Objectives.* Washington, DC: Public Health Service; DHHS publication no. (PHS) 91-50213; 1991.
14. Hall WD, Ferrario CM, Moore MA, et al. Hypertension-related morbidity and mortality in the southeastern United States. *Am J Med Sci* 1997;313:195-206. Pr
15. Banks J. *National Heart, Lung, and Blood Institute Marketing Research Study on the Formatting, Dissemination, and Use of Clinical Practice Guidelines: Executive Overview.* Bethesda, MD: National Heart, Lung, and Blood Institute; 1995.

16. Delbecq AL, Van de Ven AH, Gustafon DH. *Group Techniques for Program Planning: A Guide to Nominal Group and Delphi Processes.* Glenview, IL: Scott, Foresman and Company; 1975.

17. Last JM, Abramson JH (eds.) *A Dictionary of Epidemiology,* third edition. New York, NY: Oxford University Press; 1995.

18. Lever AF, Ramsay LE. Treatment of hypertension in the elderly. *J Hypertens* 1995;13:571-579.

19. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature. IX. A method for grading health care recommendations. *JAMA* 1995;274:1800-1804.

20. Zanchetti A, Mancia G. Editors' corner: strategies for antihypertensive treatment decisions: how to assess benefits? *J Hypertens* 1997;15:215-216.

21. Chatellier G, Ménard J. The absolute risk as a guide to influence the treatment decision-making process in mild hypertension. *J Hypertens* 1997;15:217-219.

22. Linjer E, Hansson L. Underestimation of the true benefits of antihypertensive treatment: an assessment of some important sources of error. *J Hypertens* 1997;15:221-225.

23. Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment trials of hypertension: improving the estimate of therapeutic benefit. *J Hum Hypertens* 1996;10:1-8.

24. Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the US adult population: results from the third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25:305-313. X

25. Fuster V, Pearson TA. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events, September 14-15, 1995. *J Am Coll Cardiol* 1996;27:957-1047.

26. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program working group report on hypertension in the elderly. *Hypertension* 1994;23:275-285. Pr

27. Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992;152:56-64.

28. National High Blood Pressure Education Program. *Churches as an Avenue to High Blood Pressure Control.* Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; NIH publication no. 92-2725; reprinted 1992.

29. National High Blood Pressure Education Program. *National High Blood Pressure Education Program Working Group Report on Primary Prevention of Hypertension.* Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute; NIH publication no. 93-2669, 1993. Pr

30. National Heart, Lung, and Blood Institute. *Finding Resources for Healthy Heart Programs at Work.* Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; NIH publication no. 92-737; 1992.

31. National Heart, Lung, and Blood Institute. *Minority Health Issues for an Emerging Majority: 4th National Forum on Cardiovascular Health, Pulmonary Disorders, and Blood Resources Proceedings.* Sponsored by National Heart, Lung, and Blood Institute; NHLBI Ad Hoc Committee on Minority Populations; and National Medical Association, Washington, DC; June 26-27, 1992.

32. National Heart, Lung, and Blood Institute. *The Sports Guide: NHLBI Planning Guide for Cardiovascular Risk Reduction Projects at Sporting Events.* Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; NIH publication no. 95-3802; 1995.

33. University of Maryland School of Medicine. *Control of Blood Pressure at the Workplace: University of Maryland School of Medicine.* Baltimore, MD: University of Maryland; NTIS accession no. PB83-113381; 1982.

34. Westinghouse Health Systems. *Demonstration Programs in Hypertension Control in the Work Setting: Volume I: Technical Report.* Columbia, MD: Westinghouse Health Systems; contract no. NO1-HV-82911; 1981.

35. Westinghouse Health Systems. *Demonstration Programs in Hypertension Control in the Work Setting: Volume II: Exhibits and Appendices.* Columbia, MD: Westinghouse Health Systems; NTIS accession no. PB83-113373; 1982.

36. Erfurt JC, Foote A. *Hypertension Control in the Work Setting: The University of Michigan Ford Motor Company Demonstration Program.* Springfield, VA: National Technical Information Service; NTIS accession no. PB83-113399; 1982.

37. Hill MN, Bone LR, Butz AM. Enhancing the role of community-health workers in research. *Image: Journal of Nursing Scholarship* 1996;28:221-226. Pr

38. Kotchen JM, McKean HE, Jackson-Thayer S, Moore RW, Straus R, Kotchen TA. Impact of a rural high blood pressure control program on hypertension control and cardiovascular disease mortality. *JAMA* 1986;255:2177- 2182.

39. Morisky DE, Levine DM, Green LW, Shapiro S, Russell RP, Smith CR. Five-year blood pressure control and mortality following health education for hypertensive patients. *Am J Public Health* 1983;73: 153-162.

40. Stamler J. Blood pressure and high blood pressure: aspects of risk. *Hypertension* 1991;18(suppl I):I-95–I-107. F

41. Flack JM, Neaton J, Grimm R Jr, et al., for the Multiple Risk Factor Intervention Trial Research Group. Blood pressure and mortality among men with prior myocardial infarction. *Circulation* 1995;92:2437-2445.

42. Prisant LM, Alpert BS, Robbins CB, et al. American National Standard for nonautomated sphygmomanometers: summary report. *Am J Hypertens* 1995; 8:210-213.

43. Perloff D, Grim C, Flack J, et al., for the Writing Group. Human blood pressure determination by sphygmomanometry. *Circulation* 1993;88:2460-2467.

44. American Society of Hypertension. Recommendations for routine blood pressure measurement by indirect cuff sphygmomanometry. *Am J Hypertens* 1992;5:207-209.

45. Pickering T, for an American Society of Hypertension ad hoc panel. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. *Am J Hypertens* 1995;9:1-11. Pr

46. Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood-pressure control in the hypertensive population. *Lancet* 1997;349:454-457.

47. Appel LJ, Stason WB. Ambulatory blood pressure monitoring and blood pressure self-measurement in the diagnosis and management of hypertension. *Ann Intern Med* 1993;118:867-882.

48. Tsuji I, Imai Y, Nagai K, et al. Proposal of reference values for home blood pressure measurement: prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am J Hypertens* 1997;10:409-418.

49. O'Brien E, Petrie J, Littler W, et al. The British Hypertension Society protocol for the evaluation of automated and semi-automated blood pressure measuring devices with special reference to ambulatory systems. *J Hypertens* 1990;8:607-619.

50. White WB, Berson AS, Robbins C, et al. National standard for measurement of resting and ambulatory blood pressures with automated sphygmomanometers. *Hypertension* 1993;21:504-509.

51. Nesselroad JM, Flacco VA, Phillips DM, Kruse J. Accuracy of automated finger blood pressure devices. *Fam Med* 1996;28:189-192.

52. Consumer Reports. Blood-pressure monitors: convenience doesn't equal accuracy. *Consumer Rep* 1996; 61:50,53-55.

53. Sternberg H, Rosenthal T, Shamiss A, Green M. Altered circadian rhythm of blood pressure in shift workers. *J Hum Hypertens* 1995;9:349-353.

54. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983;249:2792- 2798.

55. Perloff D, Sokolow M, Cowan RM, Juster RP. Prognostic value of ambulatory blood pressure measurements: further analyses. *J Hypertens* 1989;7(suppl 3):S3-S10.

56. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801.

57. Klein R, Klein BEK, Moss SE, Wang Q. Hypertension and retinopathy, arteriolar narrowing, and arteriovenous nicking in a population. *Arch Ophthalmol* 1994;112:92-98.

58. Newman AB, Sutton-Tyrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. *JAMA* 1993; 270:487-489.

59. Ward R. Familial aggregation and genetic epidemiology of blood pressure. In: Laragh JH, Brenner BM, (eds.). *Hypertension: Pathophysiology, Diagnosis, and Management.* New York, NY: Raven Press; 1990:81-100.

60. Lifton RP, Dluhy RG, Powers M, et al. A chimaeric 11-ß-hydroxylase/aldosterone synthase gene causes glucocorticoid-remediable aldosteronism and human hypertension. *Nature* 1992;355:262-265.

61. Lander ES, Schork NJ. Genetic dissection of complex traits. *Science* 1994;265:2037-2048.

62. WHO Expert Committee on Hypertension Control. *Hypertension Control: Report of a WHO Expert Committee,* WHO Technical Report Series no. 862. Geneva, Switzerland: World Health Organization; 1996.

63. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile: a statement for health professionals. *Circulation* 1991;83:356-362.

64. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996;275: 1571-1576. F

65. Levy D. A multifactoral approach to coronary disease risk assessment. *Clin Exp Hypertens* 1993; 15:1077-1086.

66. American Heart Association. *Welcome to the Coronary Heart Disease Risk Assessment* [Web page]. http://www.amhrt.org/risk/index.html.

67. Thürmer HL, Lund-Larsen PG, Tverdal A. Is blood pressure treatment as effective in a population setting as in controlled trials? Results from a prospective study. *J Hypertens* 1994;12:481-490. F

68. Stamler R, Stamler J, Gosch FC, et al. Primary prevention of hypertension by nutritional-hygienic means: final report of a randomized, controlled trial. *JAMA* 1989;262:1801-1807. Ra

69. Stamler J, Caggiula AW, Grandits GA. Chapter 12. Relation of body mass and alcohol, nutrient, fiber, and caffeine intakes to blood pressure in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 1997;65(suppl):338S-365S. F

70. Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. *Arch Intern Med* 1990;150:153-162. Ra

71. Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, phase I. *JAMA* 1992;267:1213-1220. Ra

72. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997;157:657-667. Ra

73. Appel LJ, Moore TJ, Obarzanek E, et al., for the DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-1124. Ra

74. Du X, Cruickshank K, McNamee R, et al. Case-control study of stroke and the quality of hypertension control in north west England. *BMJ* 1997;314:272-276. Re

75. Lazarus JM, Bourgoignie JJ, Buckalew VM, et al., for the Modification of Diet in Renal Disease Study Group. Achievement and safety of a low blood pressure goal in chronic renal disease: the Modification of Diet in Renal Disease Study Group. *Hypertension* 1997;29:641-650. Ra, F

76. Krumholz HM, Parent EM, Tu N, et al. Readmission after hospitalization for congestive heart failure among medicare beneficiaries. *Arch Intern Med* 1997;157:99-104. F

77. Neaton JD, Grimm RH Jr, Prineas RJ, et al., for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA* 1993;270:713-724. C, Ra

78. Singer DRJ, Markandu ND, Cappuccio FP, Miller MA, Sagnella GA, MacGregor GA. Reduction of salt intake during converting enzyme inhibitor treatment compared with addition of a thiazide. *Hypertension* 1995;25:1042-1044. Ra

79. Pouliot MC, Després JP, Lemieux S, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994;73: 460-468. X

80. Whelton PK, Applegate WB, Ettinger WH, et al. Efficacy of weight loss and reduced sodium intake in the Trial of Nonpharmacologic Interventions in the Elderly (TONE) [abstract]. *Circulation* 1996;94 (suppl I):I-178. Ra

81. U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996. Pr

82. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *New Engl J Med* 1997;337:581-588.

83. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 1996;335:609-616. Re

84. Puddey IB, Parker M, Beilen LJ, Vandongen R, Masarei JRL. Effects of alcohol and caloric restrictions on blood pressure and serum lipids in overweight men. *Hypertension* 1992;20:533-541. Ra

85. Gill JS, Shipley MJ, Tsementzis SA, et al. Alcohol consumption—a risk factor for hemorrhagic and non-hemorrhagic stroke. *Am J Med* 1991;90:489-497. Re

86. Frezza M, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women: the role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *New Engl J Med* 1990;322:95-99. C

87. U.S. Department of Agriculture and U.S. Department of Health and Human Services. *Nutrition and Your Health: Dietary Guidelines for Americans*, Fourth edition. Home and Garden Bulletin No. 232. Washington, DC: U.S. Department of Agriculture; 1995.

88. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993; 328:538-545. F

89. Kokkinos PF, Narayan P, Colleran JA, et al. Effects of regular exercise on blood pressure and left ventricular hypertrophy in African-American men with severe hypertension. *N Engl J Med* 1995;333:1462-1467. Ra

90. Blair SN, Goodyear NN, Gibbons LW, Cooper KH. Physical fitness and incidence of hypertension in healthy normotensive men and women. *JAMA* 1984;252:487-490. F

91. Weinberger MH. Salt sensitivity of blood pressure in humans. *Hypertension* 1996;27(part 2):481-490. Pr

92. Elliott P, Stamler J, Nichols R, et al., for the Intersalt Cooperative Research Group. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *BMJ* 1996; 312:1249-1253. X

93. Cutler JA, Follmann D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr* 1997;65(suppl):643S-651S. M

94. Midgley JP, Matthew AG, Greenwood CMT, Logan AG. Effect of reduced dietary sodium on blood pressure: a meta-analysis of randomized controlled trials. *JAMA* 1996;275:1590-1597. M

95. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension* 1995;25:1144-1152. F

96. Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. *Am J Clin Nutr* 1995;62:740-745. F

97. Ram CVS, Garrett BN, Kaplan NM. Moderate sodium restriction and various diuretics in the treatment of hypertension: effects of potassium wastage and blood pressure control. *Arch Intern Med* 1981;141: 1015-1019. Ra

98. Antonios TFT, MacGregor GA. Salt—more adverse effects. *Lancet* 1996;348:250-251. Pr

99. Cirillo M, Laurenzi M, Panarelli W, Stamler J, for the Gubbio Population Study Research Group. Urinary sodium to potassium ratio and urinary stone disease. *Kidney Int* 1994;46:1133-1139. F

100. Liebson PR, Grandits GA, Dianzumba S, et al., for the Treatment of Hypertension Study Research Group. Comparison of five antihypertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). *Circulation* 1995;91:698-706. Ra

101. Messerli FH, Schmieder RE, Weir MR. Salt—a perpetrator of hypertensive target organ disease? *Arch Intern Med* 1997;157:2449-2452. Pr

102. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure: meta- analysis of randomized controlled clinical trials. *JAMA* 1997;277:1624-1632. M

103. Cappuccio FP, Elliott P, Allender PS, Pryer J, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. *Am J Epidemiol* 1995;142:935-945. F

104. Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliott P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. *Ann Intern Med* 1996;124:825-831. M

105. Toft I, Bønaa KH, Ingebretsen OC, Nordøy A, Jenssen T. Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension: a randomized, controlled trial. *Ann Intern Med* 1995;123:911-918. Ra

106. Obarzanek E, Velletri PA, Cutler JA. Dietary protein and blood pressure. *JAMA* 1996;275:1598-1603. Pr

107. Stamler J, Elliott P, Kesteloot H, et al. Inverse relation of dietary protein markers with blood pressure: findings for 10,020 men and women in the INTERSALT study. *Circulation* 1996;94:1629-1634. F

108. van Montfrans GA, Karemaker JM, Wieling W, Dunning AJ. Relaxation therapy and continuous ambulatory blood pressure in mild hypertension: a controlled study. *BMJ* 1990;300:1368-1372. Ra

109. Alexander CN, Schneider RH, Staggers F, et al. Trial of stress reduction for hypertension in older African Americans. II. Sex and risk subgroup analysis. *Hypertension* 1996;28:228-237. Ra

110. Greenberg G, Thompson SG, Brennan PJ. The relationship between smoking and the response to antihypertensive treatment in mild hypertensives in the Medical Research Council's trial of treatment. *Int J Epidemiol* 1987;16:25-30. F

111. U.S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General.* Rockville, MD: Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; DHHS publication no. (CDC) 90-8416; 1990. Pr

112. Agency for Health Care Policy and Research. *You Can Quit Smoking: Consumer Guide.* Washington, DC: U.S. Department of Health and Human Services; AHCPR publication no. 96-0695; 1996.

113. American Heart Association. *Calling It Quits.* Dallas, TX: American Heart Association; 1984.

114. American Lung Association. *Helping Smokers Get Ready To Quit.* New York, NY: American Lung Association; 1991.

115. U.S. Department of Health and Human Services. *"I Quit"—What To Do When You're Sick of Smoking, Chewing, or Dipping.* Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1997.

116. Khoury Z, Comans P, Keren A, Lerer T, Gavish A, Tzivoni D. Effects of transdermal nicotine patches on ambulatory ECG monitoring findings: a double-blind study in healthy smokers. *Cardiovasc Drugs Ther* 1996;10:179-184. Re

117. Stamler J, Rains-Clearman D, Lenz-Litzow K, Tillotson JL, Grandits GA. Chapter 14. Relation of smoking at baseline and during trial years 1-6 to food and nutrient intakes and weight in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 1997;65(suppl):374S-402S. F

118. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA* 1997;277:739-745. M

119. Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 1996;27:1214-1218. Pr

120. MacMahon S, Rodgers A. The effects of blood pressure reduction in older patients: an overview of five randomized controlled trials in elderly hypertensives. *Clin Exp Hypertens* 1993;15:967-978. M

121. Frishman WH, Bryzinski BS, Coulson LR, et al. A multifactorial trial design to assess combination therapy in hypertension: treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med* 1994;154: 1461-1468. Ra

122. Epstein M, Bakris G. Newer approaches to antihypertensive therapy: use of fixed-dose combination therapy. *Arch Intern Med* 1996;156:1969-1978. Pr

123. Gradman AH, Cutler NR, Davis PJ, Robbins JA, Weiss RJ, Wood BC, for the Enalapril-Felodipine ER Factorial Study Group. Combined enalapril and felodipine extended release (ER) for systemic hypertension. *Am J Cardiol* 1997;79:431-435. Ra

124. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 1996;276:1328-1331. Pr

125. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995;92:1326-1331. M

126. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997;15:105-115. Pr

127. Psaty BM, Furberg CD. Clinical implications of the WHO/ISH statement on calcium antagonists. *J Hypertens* 1997;15:1197-1200.

128. Gueyffier F, Boutitie F, Boissel JP, et al., for the INDANA Investigators. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: a meta-analysis of individual patient data from randomized, controlled trials. *Ann Intern Med* 1997;126:761-767. M

129. Materson BJ, Reda DJ, Cushman WC, et al., for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Single-drug therapy for hypertension in men: a comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993;328:914-921. Ra

130. Grimm RH Jr, Grandits GA, Cutler JA, et al., for the TOMHS Research Group. Relationships of quality-of-life measures to long-term lifestyle and drug treatment in the Treatment of Mild Hypertension Study. *Arch Intern Med* 1997;157:638-648. Ra

131. Edelson JT, Weinstein MC, Tosteson ANA, Williams L, Lee TH, Goldman L. Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. *JAMA* 1990;263:407-413. Pr

132. Jönsson BG. Cost-benefit of treating hypertension. *J Hypertens* 1994;12(suppl 10):S65-S70. Pr

133. Johannesson M. The cost effectiveness of hypertension treatment in Sweden. *PharmacoEconomics* 1995; 7:242-250. Pr

134. Kaplan NM, Gifford RW Jr. Choice of initial therapy for hypertension. *JAMA* 1996;275:1577-1580. Pr

135. Materson BJ, Reda DJ, Preston RA, et al., for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Response to a second single antihypertensive agent used as monotherapy for hypertension after failure of the initial drug. *Arch Intern Med* 1995;155:1757-1762. F

136. Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension: is there a point beyond which pressure reduction is dangerous? *JAMA* 1991;265:489-495. Pr

137. Coope J, Warrender TS. Randomised trial of treatment of hypertension in elderly patients in primary care. *Br Med J* 1986;293:1145-1151. F

138. Staessen J, Bulpitt C, Clement D, et al. Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. *Br Med J* 1989;298:1552-1556. F

139. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* 1994;23:395-401. F

140. Staessen JA, Fagard R, Thijs L, et al., for the Systolic Hypertension—Europe (Syst-Eur) Trial Investigators. Morbidity and mortality in the placebo-controlled European Trial on Isolated Systolic Hypertension in the Elderly. *Lancet* 1997;350:757-764. Ra

141. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994;50:272-298. Pr

142. Systolic Hypertension in the Elderly Program Cooperative Research Group. Implications of the Systolic Hypertension in the Elderly Program. *Hypertension* 1993;21:335-343. Ra

143. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action; a statement for healthcare professionals. *Circulation* 1997;95:1085-1090. Pr

144. Schultz JF, Sheps SG. Management of patients with hypertension: a hypertension clinic model. *Mayo Clin Proc* 1994;69:997-999. Pr

145. Setaro JF, Black HR. Refractory hypertension. *N Engl J Med* 1992;327:543-547. Pr

146. U.S. Bureau of the Census, Population Division. *Estimates From the 1990 Census.* Washington, DC: U.S. Bureau of the Census; 1996. X

147. Fang J, Madhavan S, Alderman MH. The association between birthplace and mortality from cardiovascular causes among black and white residents of New York City. *N Engl J Med* 1996;335:1545-1551. F

148. Havas S, Sherwin R. Putting it all together: summary of the NHLBI Workshop on the Epidemiology of Hypertension in Hispanic American, Native American, and Asian/Pacific Islander American Populations. *Public Health Rep* 1996;3(suppl 2):77-79. Pr

149. Chen MF, Chen CC, Chen WJ, Wu CC, Liau CS, Lee YT. Dose titration study of isradipine in Chinese patients with mild to moderate essential hypertension. *Cardiovasc Drugs Ther* 1993;7;133-138. C

150. Chen MF, Yang CY, Chen WJ, et al. A double-blind comparison of once-daily metoprolol controlled-release and atenolol in the treatment of Chinese patients with mild to moderate hypertension. *Cardiovasc Drugs Ther* 1995;9:401-406. X

151. Enas EA, Garg A, Davidson MA, Nair VM, Huet BA, Yusuf S. Coronary heart disease and its risk factors in first-generation immigrant Asian Indians to the United States of America. *Indian Heart J* 1996; 48:343-353. X

152. Howard BV, Lee ET, Yeh JL, et al. Hypertension in adult American Indians: the Strong Heart Study. *Hypertension* 1996;28:256-264. X

153. Winkleby MA, Kraemer H, Lin J, Jatulis D, Fortmann SP. Sociodemographic influences on Hispanic-white differences in blood pressure. *Public Health Rep* 1996;111(suppl 2):30-32. X

154. Singh GK, Kochanek KD, MacDorman MF. Advance report of final mortality statistics, 1994. *Mon Vital Stat Rep* 1996;45(3, suppl):1-76. X

155. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. End-stage renal disease in African-American and white men: 16-year MRFIT findings. *JAMA* 1997;277:1293-1298. F

156. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: mortality by race-sex and blood pressure level: a further analysis. *J Community Health* 1984;9:314-327. Ra

157. Ooi WL, Budner NS, Cohen H, Madhavan S, Alderman MH. Impact of race on treatment response and cardiovascular disease among hypertensives. *Hypertension* 1989;14:227-234. F

158. Townsend RR, DiPette DJ, Goodman R, et al. Combined α/β-blockade versus α_1-selective blockade in essential hypertension in black and white patients. *Clin Pharmacol Ther* 1990;48:665-675. Ra

159. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302. Ra

160. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 task force report on high blood pressure in children and adolescents: a working group report from the National High Blood Pressure Education Program. *Pediatrics* 1996;98:649-658. Pr

161. Woods JW. Oral contraceptives and hypertension. *Hypertension* 1988;11(suppl II):II-11–II-15. Pr

162. Sibai BM. Treatment of hypertension in pregnant women. *New Engl J Med* 1996;335:257-265. Pr

163. Lindheimer MD. Pre-eclampsia—eclampsia 1996: preventable? Have disputes on its treatment been resolved? *Curr Opin Nephrol Hypertens* 1996;5:452-458. Pr

164. Levine RJ, for the CPEP Study Group. Calcium for preeclampsia (CPEP): a double-blind, placebo-controlled trial in healthy nulliparas. *N Engl J Med* 1997;337:69-76. Pr

165. National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. National High Blood Pressure Education Program working group report on high blood pressure in pregnancy. *Am J Obstet Gynecol* 1990;163:1689-1712. Pr

166. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1995;273:199-208. Ra

167. Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. *N Engl J Med* 1993;329:1912-1917. F

168. Messerli FH. Osler's maneuver, pseudohypertension, and true hypertension in the elderly. *Am J Med* 1986;80:906-910.

169. Wiinberg N, Høegholm A, Christensen HR, et al. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. *Am J Hypertens* 1995;8:978-986. X

170. Ooi WL, Barrett S, Hossain M, Kelley-Gagnon M, Lipsitz LA. Patterns of orthostatic blood pressure change and their clinical correlates in a frail, elderly population. *JAMA* 1997;277:1299-1304. X

171. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-3264. Ra

172. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992;304:405-412. Ra, F

173. Dahlöf B, Lindholm LH, Hansson L, Scherstén B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281-1285. Ra

174. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1997;278:212-216. Ra

175. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-1587. C

176. Hennekens CH, Albert CM, Godfried SL, Gaziano JM, Buring JE. Adjunctive drug therapy of acute myocardial infarction—evidence from clinical trials. *N Engl J Med* 1996;335:1660-1667. Pr

177. Smith SC Jr, Blair SN, Criqui MH, et al., for the Secondary Prevention Panel. Preventing heart attack and death in patients with coronary disease. *J Am Coll Cardiol* 1995;26:292-294. Pr

178. Alderman MH, Cohen H, Roqué R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet* 1997;349:594-598. Re

179. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;274:620-625. Re

180. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1996;28:1328-1428. Pr

181. Gibson RS, Boden WE. Calcium channel antagonists: friend or foe in postinfarction patients? *Am J Hypertens* 1996;9:172S-176S. Pr

182. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114:345-352. F

183. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. *JAMA* 1995;273: 1592-1597. F

184. Devereux RB. Do antihypertensive drugs differ in their ability to regress left ventricular hypertrophy? *Circulation* 1997;95:1983-1985. Pr

185. Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ, for the VA Cooperative Study Group on Antihypertensive Agents. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension: comparison of six antihypertensive agents; the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Circulation* 1997;95:2007-2014. Ra

186. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994;90:1786-1793. F

187. Devereux RB, Agabiti-Rosei E, Dahlöf B, et al. Regression of left ventricular hypertrophy as a surrogate end-point for morbid events in hypertension treatment trials. *J Hypertens* 1996;14(suppl 2):S95-S102. Pr

188. Frohlich ED. Pathophysiology of systemic arterial hypertension. In: Schlant RC, Alexander RW, O'Rourke RA, Roberts R, Sonnenblick EH (eds.). *Hurst's The Heart*, eighth edition. New York, NY: McGraw-Hill; 1993:1391-1401. Pr

189. Sheps SG, Frohlich ED. Limited echocardiography for hypertensive left ventricular hypertrophy. *Hypertension* 1997;29:560-563. Pr

190. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure: a clinical mechanistic overview. *Arch Intern Med* 1996;156:1789-1796. Pr

191. Pfeffer MA, Braunwald E, Moyé LA, et al., for the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trials. *N Engl J Med* 1992;327:669-677. Ra

192. Garg R, Yusuf S, for the Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-1456. M

193. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *New Engl J Med* 1986;314: 1547-1542. Ra

194. Packer M, Bristow MR, Cohn JN, et al., for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334: 1349-1355. Ra

195. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;349:375-380. Ra

196. Pitt B, Segal R, Martinez FA, et al., for the ELITE Study Investigators. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-752. Ra

197. Packer M, O'Connor CM, Ghali JK, et al., for the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *New Engl J Med* 1996;335:1107-1114. Ra

198. Cohn JN, Ziesche S, Smith R, et al., for the Vasodilator-Heart Failure Trial. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. *Circulation* 1997;96:856-863. Ra

199. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension: results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 1967;202:1028-1034. Ra

200. Preston RA, Singer I, Epstein M. Renal parenchymal hypertension: current concepts of pathogenesis and management. *Arch Intern Med* 1996;156:602-611. Pr

201. Fogo A, Smith MC, Cleveland W, Debruge J, Agodoa L, for the AASK Pilot Investigators. Renal biopsy findings in the African-American Study of Kidney Disease (AASK) [abstract]. *J Am Soc Nephrol* 1994;5:560. X

202. Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 1995;25:587-594. F

203. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *New Engl J Med* 1996;334:13-18. F

204. National High Blood Pressure Education Program Working Group. 1995 update of the working group reports on chronic renal failure and renovascular hypertension. *Arch Intern Med* 1996;156:1938-1947. Pr

205. Bakris GL, Mangrum A, Copley JB, Vicknair N, Sadler R. Effect of calcium channel or β-blockade on the progression of diabetic nephropathy in African Americans. *Hypertension* 1997;29:744-750. Pr

206. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD, for the Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-1462. Ra

207. Klahr S, Levey AS, Beck GJ, et al., for the Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994;330:877-884. Ra

208. Maschio G, Alberti D, Janin G, et al., for the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996;334:939-945. Ra

209. Giatras I, Lau J, Levey AS, for the Angiotensin-Converting Enzyme Inhibition and Progressive Renal Disease Study Group. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. *Ann Intern Med* 1997;127:337-345. M

210. Textor SC. Renal failure related to angiotensin-converting enzyme inhibitors. *Semin Nephrol* 1997; 17:67-76. Pr

211. Appel RG, Bleyer AJ, Reavis S, Hansen KJ. Renovascular disease in older patients beginning renal replacement therapy. *Kidney Int* 1995;48:171-176. F

212. Vidt DG. Cholesterol emboli: a common cause of renal failure. *Annu Rev Med* 1997;48:375-385. Pr

213. Bonelli FS, McKusick MA, Textor SC, et al. Renal artery angioplasty: technical results and clinical outcome in 320 patients. *Mayo Clin Proc* 1995;70: 1041-1052. Re

214. Sos TA. Angioplasty for the treatment of azotemia and renovascular hypertension in atherosclerotic renal artery disease. *Circulation* 1991;83(suppl I): I-162–I-166. Pr

215. Harden PN, MacLeod MJ, Rodger RSC, et al. Effect of renal-artery stenting on progression of renovascular renal failure. *Lancet* 1997;349:1133-1136. C

216. Zierler RE, Bergelin RO, Davidson RC, Cantwell-Gab K, Polissar NL, Strandness DE Jr. A prospective study of disease progression in patients with atherosclerotic renal artery stenosis. *Am J Hypertens* 1996;9:1055-1061. F

217. American Diabetes Association. American Diabetes Association: clinical practice recommendations. *Diabetes Care* 1997;20(suppl):S1-S70. Pr

218. National High Blood Pressure Education Program Working Group. National High Blood Pressure Education Program working group report on hypertension in diabetes. *Hypertension* 1994;23:145-158. Pr

219. Curb JD, Pressel SL, Cutler JA, et al., for the Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886-1892. Ra

220. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 1997;278:40-43. Re

221. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 1996;156:286-289. Ra

222. Kasiske BL, Kalil RSN, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: A meta-regression analysis. *Ann Intern Med* 1993;118:129-138. M

223. Bakris GL, Copley JB, Vicknair N, Sadler R, Leurgans S. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int* 1996;50:1641-1650. Ra

224. Velussi M, Brocco E, Frigato F, et al. Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 1996;45:216-222. Ra

225. Reaven GM, Lithell H, Landsberg L. Hypertension and associated metabolic abnormalities—the role of insulin resistance and the sympathoadrenal system. *New Engl J Med* 1996;334:374-381. Pr

226. Kotchen TA. Attenuation of hypertension by insulin-sensitizing agents. *Hypertension* 1996;28:219-223. Pr

227. Working Group on Management of Patients With Hypertension and High Blood Cholesterol. National education programs working group report on the management of patients with hypertension and high blood cholesterol. *Ann Intern Med* 1991;114:224-237. Pr

228. Kasiske BL, Ma JZ, Kalil RSN, Louis TA. Effects of antihypertensive therapy on serum lipids. *Ann Intern Med* 1995;122:133-141. Pr

229. Stamler J, Briefel RR, Milas C, Grandits GA, Caggiula AW. Relation of changes in dietary lipids and weight, trial years 1-6, to changes in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial. *Am J Clin Nutr* 1997;65(suppl):272S-288S. F

230. Grimm RH Jr, Flack JM, Grandits GA, et al., for the Treatment of Mild Hypertension Study (TOMHS) Research Group. Long-term effects on plasma lipids of diet and drugs to treat hypertension. *JAMA* 1996;275:1549-1556. Ra, F

231. Frost PH, Davis BR, Burlando AJ, et al., for the Systolic Hypertension in the Elderly Research Group. Serum lipids and incidence of coronary heart disease: findings from the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 1996;94:2381-2388. F

232. Curb JD, Maxwell MH, Schneider KA, Taylor JO, Shulman NB. Adverse effects of antihypertensive medications in the Hypertension Detection and Follow-up Program. *Prog Cardiovasc Dis* 1986;29(suppl 1):73-88. F

233. Lind L, Pollare T, Berne C, Lithell H. Long-term metabolic effects of antihypertensive drugs. *Am Heart J* 1994;128:1177-1183. F

234. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-371. M

235. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-1009. Ra

236. Shepherd J, Cobbe SM, Ford I, et al., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-1307. Ra

237. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389. Ra

238. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* 1997;278:313-321. M

239. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994;89:1329-1445. Pr

240. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990;336:261-264. Re

241. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea: experience in 385 male patients. *Chest* 1988;94:9-14. F

242. Sanders BP, Portman RJ, Ramey RA, Hill M, Strunk RC. Hypertension during reduction of long-term steroid therapy in young subjects with asthma. *J Allergy Clin Immunol* 1992;89:816-821. F

243. Langford HG, Blaufox MD, Borhani NO, et al., on behalf of the Hypertension Detection and Follow-up Cooperative Group. Is thiazide-produced uric acid elevation harmful? Analysis of data from the Hypertension Detection and Follow-up Program. *Arch Intern Med* 1987;147:645-649. F

244. Eagle KA, Brundage BH, Chaitman BR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 1996;27: 910-948. Pr

245. Riles TS, Fisher FS, Schaefer S, Pasternack PF, Baumann FG. Plasma catecholamine concentrations during abdominal aortic aneurysm surgery: the link to perioperative myocardial ischemia. *Ann Vasc Surg* 1993;7:213- 219.

246. Mangano DT, Layug EL, Wallace A, Tateo I, for the Multicenter Study of Perioperative Ischemia Research Group. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996;335:1713-1720. Ra

247. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996;347:1061-1065. F

248. Zuccalà G, Pahor M, Landi F, et al. Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture: observational study. *BMJ* 1997;314:643-644. C

249. Brecklin C, Gopaniuk A, Kravetz T, et al. Chronic cocaine abuse causes acute but not chronic hypertension [abstract]. *J Am Soc Nephrol* 1996;7:1547.

250. Herzlich BC, Arsura EL, Pagala M, Grob D. Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988;109:335-336.

251. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995;333: 1267-1272. X

252. Lange RA, Cigarroa RG, Flores ED, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. *Ann Intern Med* 1990;112:897-903. Ra

253. Textor SC, Taler SJ, Canzanello VJ, Schwartz L. Cyclosporine, blood pressure and atherosclerosis. *Cardiology in Review* 1997;5:141-151. Pr

254. Grossman E, Messerli FH. High blood pressure: a side effect of drugs, poisons, and food. *Arch Intern Med* 1995;155;450-460.

APPENDIX A

National Institutes of Health

The DASH Diet

This eating plan is from the "Dietary Approaches to Stop Hypertension" (DASH) clinical study. The research was funded by the National Heart, Lung, and Blood Institute (NHLBI), with additional support by the National Center for Research Resources and the Office of Research on Minority Health, all units of the National Institutes of Health. The final results of the DASH study appear in the April 17, 1997, issue of the *New England Journal of Medicine*. The results show that the DASH "combination diet" lowered blood pressure and, so, may help prevent and control high blood pressure.

The "combination diet" is rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fat. It also is low in cholesterol; high in dietary fiber, potassium, calcium, and magnesium; and moderately high in protein.

The DASH eating plan shown below is based on 2,000 calories a day. Depending on your caloric needs, your number of daily servings in a food group may vary from those listed.

Food Group	Daily Servings	Serving Sizes	Examples and Notes	Significance of Each Food Group to the DASH Diet Pattern
Grains and grain products	7-8	1 slice bread 1/2 C dry cereal 1/2 C cooked rice, pasta, or cereal	whole wheat bread, English muffin, pita bread, bagel, cereals, grits, oatmeal	major sources of energy and fiber
Vegetables	4-5	1 C raw leafy vegetable 1/2 C cooked vegetable 6 oz vegetable juice	tomatoes, potatoes, carrots, peas, squash, broccoli, turnip greens, collards, kale, spinach, artichokes, beans, sweet potatoes	rich sources of potassium, magnesium, and fiber
Fruits	4-5	6 oz fruit juice 1 medium fruit 1/4 C dried fruit 1/4 C fresh, frozen, or canned fruit	apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, prunes, raisins, strawberries, tangerines	important sources of potassium, magnesium, and fiber
Low-fat or nonfat dairy foods	2-3	8 oz milk 1 C yogurt 1.5 oz cheese	skim or 1% milk, skim or low-fat buttermilk, nonfat or low-fat yogurt, part-skim mozzarella cheese, nonfat cheese	major sources of calcium and protein
Meats, poultry, and fish	2 or less	3 oz cooked meats, poultry, or fish	select only lean; trim away visible fats; broil, roast, or boil, instead of frying; remove skin from poultry	rich sources of protein and magnesium
Nuts, seeds, and legumes	4-5 per week	1.5 oz or 1/3 C nuts 1/2 oz or 2 Tbsp seeds 1/2 C cooked legumes	almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils	rich sources of energy, magnesium, potassium, protein, and fiber

Turn the page for a sample menu using the DASH diet.

APPENDIX A (CONTINUED)

National Institutes of Health

The DASH Diet • Sample Menu • based on 2,000 calories/day

Food	Amount	Servings Provided
Breakfast		
orange juice	6 oz	1 fruit
1% low-fat milk	8 oz (1 C)	1 dairy
corn flakes (with 1 tsp sugar)	1 C	2 grains
banana	1 medium	1 fruit
whole wheat bread (with 1 Tbsp jelly)	1 slice	1 grain
soft margarine	1 tsp	1 fat
Lunch		
chicken salad	3/4 C	1 poultry
pita bread	1/2, large	1 grain
raw vegetable medley:		
carrot and celery sticks	3-4 sticks each	
radishes	2	1 vegetable
loose-leaf lettuce	2 leaves	
part-skim mozzarella cheese	1.5 slice (1.5 oz)	1 dairy
1% low-fat milk	8 oz (1 C)	1 dairy
fruit cocktail in light syrup	1/2 C	1 fruit
Dinner		
herbed baked cod	3 oz	1 fish
scallion rice	1 C	2 grains
steamed broccoli	1/2 C	1 vegetable
stewed tomatoes	1/2 C	1 vegetable
spinach salad:		
raw spinach	1/2 C	
cherry tomatoes	2	1 vegetable
cucumber	2 slices	
light Italian salad dressing	1 Tbsp	1/2 fat
whole wheat dinner roll	1 small	1 grain
soft margarine	1 tsp	1 fat
melon balls	1/2 C	1 fruit
Snacks		
dried apricots	1 oz (1/4 C)	1 fruit
mini-pretzels	1 oz (3/4 C)	1 grain
mixed nuts	1.5 oz (1/3 C)	1 nuts
diet ginger ale	12 oz	0

Total number of servings in 2,000 calories/day menu:

Food Group	*Servings*
Grains	= 8
Vegetables	= 4
Fruits	= 5
Dairy Foods	= 3
Meats, Poultry, and Fish	= 2
Nuts, Seeds, and Legumes	= 1
Fats and Oils	= 2.5

Tips on Eating the DASH Way

- Start small. Make gradual changes in your eating habits.
- Center your meal around carbohydrates, such as pasta, rice, beans, or vegetables
- Treat meat as one part of the whole meal, instead of the focus.
- Use fruits or low-fat, low-calorie foods such as sugar-free gelatin for desserts and snacks.

REMEMBER! If you use the DASH diet to help prevent or control high blood pressure, make it part of a lifestyle that includes choosing foods lower in salt and sodium, keeping a healthy weight, being physically active, and, if you drink alcohol, doing so in moderation.

To learn more about high blood pressure, call 1-800-575-WELL or visit the NHLBI Web site at http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm. DASH is also online at http://dash.bwh.harvard.edu.

Index of Key Terms

High Blood Pressure Reports and Materials From the National Heart, Lung, and Blood Institute

Contact the NHLBI Information Center for the price and availability of the publications listed below.

NHLBI Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Telephone: (301) 251-1222
Fax: (301) 251-1223

Update of the Task Force Report on High Blood Pressure in Children and Adolescents. Includes revised normative blood pressure charts based on height percentiles, age, and gender beginning at 1 year of age. Also includes new charts for selecting antihypertensive drug therapy. (#3790)

Working Group Report on Primary Prevention of Hypertension. Examines the causes of high blood pressure and recommends prevention measures. Discusses sodium intake, weight, alcohol consumption, physical activity, and stress in relationship to the development of hypertension. (#2669)

Working Group Report on Hypertension in Diabetes. Guides clinicians in the care of persons with hypertension and diabetes. Addresses epidemiological, diagnostic, and clinical considerations as well as special concerns, such as kidney disease, sexual dysfunction, obesity, and pregnancy. (#3530)

Controlling High Blood Pressure in Older Women: Clinical Reference Manual. Assists clinicians in the care of older patients with high blood pressure, especially women. Presents the benefits of antihypertensive therapy, detection, evaluation, and treatment strategies. Includes charts to help clinicians improve patient adherence to therapy and select antihypertensive drug therapy. (#55-851)

1995 Update of the Working Group Reports on Chronic Renal Failure and Renovascular Hypertension. Alerts clinicians to the increasing annual incidence of end-stage renal disease (ESRD) and reviews the current knowledge about high blood pressure and chronic renal failure. Discusses therapeutic strategies to reduce the risk of ESRD, hypertensive nephrosclerosis, diabetes, and other forms of chronic renal failure. (#3791)

Enhance Your Patient Education With NHLBI High Blood Pressure Materials

High Blood Pressure: Treat It for Life. Helps patients take action against high blood pressure, including losing weight if overweight, increasing physical activity, choosing foods lower in salt and sodium, limiting alcohol, and taking medication as prescribed. Includes a sample walking program, menu ideas, and recipes. (#3312)

Eat Right To Help Lower Your High Blood Pressure. Presents practical information in an easy-to-read (5th-grade level) conversational text brochure featuring large type and colorful illustrations. Helps patients reduce high blood pressure by losing weight, being more active, drinking less alcohol, and using less salt and sodium. (#3289)

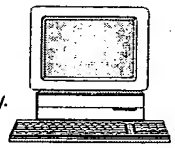
Controlling High Blood Pressure: A Woman's Guide. Explains how high blood pressure affects women's health and describes the simple steps used to prevent and control high blood pressure as well as the types of medication used to treat the condition. Includes a handy table of generic names of blood pressure medications and a chart for recording blood pressure readings. (#55-820)

Healthy Heart Handbook for Women. Tells women of all ages (both with and without heart disease) how to take action to make their hearts healthier. Discusses how to talk to the doctor, blood pressure and blood cholesterol, physical activity, weight loss, hormone replacement therapy, heart attack symptoms, heart-healthy eating, and more. (#2720)

Exercise and Your Heart—A Guide to Physical Activity. Provides patients with information on the effects of physical activity on their heart, and practical guidelines for starting and staying on their own exercise program. Discusses the benefits, risks, and common myths about exercise and includes tips and sample activity programs. (#1677)

Facts About How To Prevent High Blood Pressure. Describes what high blood pressure is and what happens when blood pressure is high. Includes information on the steps to take to prevent high blood pressure including a sample walking program, food selection and preparation tips, and weight control. (#3281)

Stay Up-to-Date Online



- Visit our Web site at www.nhlbi.nih.gov/nhlbi/nhlbi.htm.
- Learn of new publications as they become available by joining our Listserv. To join:
  1. Address an e-mail message to LISTSERV@LIST.NIH.GOV. No subject is necessary.
  2. In the body of the message, type SUBSCRIBE NHLBIINFO-L.
  3. A confirmation will be sent to you. When the confirmation is received, send a reply message and type OK in the body of the reply.

Also for Your Patients

The NHLBI Information Center offers a toll-free service (1-800-575-WELL) that features messages in Spanish or English about the prevention of high blood pressure and high blood cholesterol. The service allows callers to leave their name and address if they would like to receive additional information on these topics by mail.